Chapter

High-Density Lipoprotein: From Biological Functions to Clinical Perspectives

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Abstract

High-density lipoprotein (HDL) is a heterogeneous particle composed of apolipoproteins, enzymes, and lipids. Besides transporting cholesterol to the liver, HDL also exerts many protections on anti-oxidation, anti-inflammation, and anti-apoptosis. Initial understandings of HDL came from its protective roles against atherosclerosis and the observation that high plasma HDL cholesterol (HDL-C) levels seemed to decrease cardiovascular disease (CVD) attack. However, those patients either with cholesterol ester transfer protein (CETP) deficiency or taking CETP inhibitors substantially elevated HDL-C levels but did not necessarily decrease CVD risk. Thus, some researchers suggested that quantitative measurements of HDL particle (HDL-P) might be more valuable than traditional HDL-C measurements. What is more bewildering is that HDL from patients with systemic inflammation decreased its protective effects and even became a pro-inflammatory factor. Recently, synthesized HDL and apolipoprotein mimetic peptides showed biological functions similar to native ones. Expectedly, lots of novel measurement methods and therapeutic agents about HDL would be established soon.

Keywords: HDL, apolipoprotein, mimetic peptide, atherosclerosis, CVD

1. Introduction

Initial understandings of high-density lipoprotein (HDL) came from the epidemiological studies, which consistently showed that a low HDL cholesterol (HDL-C) level is regarded as an independent risk for the development of cardiovascular disease (CVD) [1, 2]. Inversely, elevated HDL-C concentration in plasma is correlated with reduced CVD risk [3]. Therefore, lots of strategies for raising HDL-C were considered to be the suitable targets for CVD prevention and treatment [4, 5]. Deficiency and inhibition of cholesterol ester transfer protein (CETP) increase plasma HDL-C levels; however, they do not necessarily reduce CVD risk as expected, which suggest that the compositions and functions of HDL are more complicated than we supposed before [6]. Besides reverse cholesterol transport (RCT), HDL possesses anti-oxidative, anti-inflammatory, and anti-apoptotic effects on endothelial cells, exerts anti-migrative and anti-proliferative functions on smooth muscle cells, and presents anti-development and anti-metastasis characteristics on cancer cells [7, 8]. Nevertheless, HDL either modified by oxidation and glycation or isolated from patients with systemic inflammation decreases its

protective effects and even becomes a pro-inflammatory, pro-oxidative, and pro-apoptotic factor [9]. Consequently, the question whether HDL-C is still the "good cholesterol" becomes more bewildering to be answered.

2. HDL-C levels and CVD

For a half century, Framingham study has supported the concept that HDL-C was thought to be a "good" lipoprotein and a negative risk factor against atherosclerosis and a decreased HDL-C level emerged as an independent risk for CVD, owing to a strong inverse correlation between plasma HDL-C levels and CVD [1]. The basis of this concept mainly came from the role of HDL in RCT [10]. However, the understanding of HDL-C and its relationship to CVD has changed dramatically. Deficiency and inhibition of CEPT or mutation of scavenger receptor class B type I (SR-BI) increase plasma HDL-C levels but do not accordingly reduce CVD events in these patients, which challenge the traditional ideas.

2.1 Reverse cholesterol transport (RCT)

An excess of cholesterol production or absorption is deleterious by contributing to cholesterol accumulation in vessel wall and subsequent atherosclerosis initiation. Thus, there is a physiological need to move the excessive cholesterol from peripheral tissues; this process is called reverse cholesterol transport (RCT) [10]. RCT represents the primary mechanism by which HDL delivers cholesterol from peripheral cells to the liver. This pathway of recycling and eliminating cholesterol is the antiatherogenic basis of high HDL-C levels against CVD and also represents a rescue mechanism for atherosclerotic plaque regression.

The first step of RCT is cellular cholesterol efflux to apolipoprotein A-I (apoA-I) mediated by ATP-binding cassette transporter A1 (ABCA1). Cholesterol efflux also occurs toward mature HDL through ATP-binding cassette transporter G1 (ABCG1) and SR-BI. Cholesteryl esters (CE) of HDL can be transferred to apolipoprotein B (apoB)-containing lipoproteins through the action of CETP, with ultimate uptake by low-density lipoprotein (LDL) receptor (LDL-R) in the liver. Each step in this process may influence the plasma levels of HDL-C. Because of the failure of reducing CVD risk by elevating HDL-C, the cholesterol efflux capacity of HDL seems to be more valuable to predict CVD incidence than HDL-C levels [11].

2.2 ATP-binding cassette transporter A1/G1 (ABCA1/G1)

A major breakthrough in understanding the mechanisms of RCT came from the discovery of Tangier disease, which is characterized by low HDL-C levels and high CVD risk because of the molecular defect in ABCA1 [12]. Low HDL-C level in these patients is caused by decreased cellular cholesterol efflux owing to ABCA1 mutation as well as increased catabolism of lipid-poor apoA-I [13]. ABCA1 knockout mice have an extremely low HDL-C phenotype similar to that of Tangier disease patients [14]. Thus, ABCA1 is essential for HDL maturation. In addition, it is also worth noting that the interaction between apoA-I and ABCA1 in macrophages also displays significant anti-inflammatory effects through activating JAK2/STAT3 pathway [15]. These effects reduce the attraction of macrophages into the vessel wall and ultimately result in the decreased plaque formation. These findings implicated that ABCA1 is a direct molecular link between the cardio-protective effects of cholesterol export and the inhibition of inflammatory responses in macrophages.

In contrast to ABCA1, ABCG1 promotes cholesterol efflux from macrophages to mature HDL but not to apoA-I [16]. In addition, ABCG1 also stimulates the release of cellular phospholipids to HDL [17]. Therefore, ABCA1 and ABCG1 are assumed to act in a sequential manner, which generates nascent HDL through ABCA1 and then facilitates cholesterol efflux via ABCG1, resulting in the formation of mature HDL.

2.3 Lecithin: cholesterol acyltransferase (LCAT)

LCAT is responsible for the esterification of free cholesterol and thus for the maturation of HDL by transferring fatty acids from lecithin (phosphatidyl choline) to cholesterol [18]. Once esterified, cholesterol moves from the surface to the hydrophobic core of HDL. In the presence of LCAT, the bidirectional movement of cholesterol between cells and HDL results in cholesterol efflux. Therefore, LCAT plays a central role in the initial step of RCT.

As a result of cholesterol esterification, LCAT also maintains a gradient of free cholesterol between cell membranes and lipoproteins. The activity of LCAT is essential to maintain the normal HDL metabolism and the optimal functional properties of HDL particles. In human, LCAT deficiency is responsible for low HDL-C levels, which changes HDL distribution and composition [19]. HDL from transgenic mice overexpressing human LCAT is prior to accepting free cholesterol from fibroblast compared to control HDL. It is likely that LCAT-mediated changes in HDL composition favor cholesterol accommodation within the particles. The flux of CE to the liver is increased in human LCAT-transgenic mice as a result of increased CE content in HDL but not an increased catabolic rate of HDL [20]. Although it is clear that LCAT deficiency in human and mice is associated with reduced HDL-C levels, it is still not defined whether LCAT overexpression or deficiency is pro- or anti-atherogenesis.

2.4 Cholesterol ester transfer protein (CETP)

CETP plays a key role in the exchange of CE and triglycerides (TG) between HDL and apoB-containing lipoproteins (VLDL, IDL, and LDL). As a result of CETP activation, HDL becomes smaller and TG-enriched. It is estimated that 66% of CE in HDL returns to the liver through CETP, indicating an important role of CETP in RCT process and HDL remodeling [21]. Some studies found that deficiency of CETP in human is associated with increased plasma HDL-C levels but inversely displays a relatively increased CVD incidence [22]. Small HDL particles are not increased in CETP-deficient subjects, suggesting that ABCA1-mediated cholesterol efflux might not represent the predominant pathway of cellular cholesterol efflux. Earlier studies also demonstrated that HDL from CETP-deficient subjects is defective to mediate cholesterol efflux from cholesterol-loaded macrophages, leading to the hypothesis that enrichment of CE in HDL in homozygous subjects might not be favorable for the antiatherogenic activities of these particles [23]. However, HDL from CETP-deficient subjects has been shown to possess an increased capacity to mediate cholesterol efflux through ABCG1 [24].

Additionally, inhibition of CETP successfully elevates HDL-C levels and decreases LDL-C levels but unexpectedly does not show atheroprotections and even increases cardiovascular mortality [25–27]. Until now, almost all CETP inhibitors, including torcetrapib (Pfizer), dalcetrapib (RO4607381, Roche; JTT-705, JT), anacetrapib (MK-0859, Merck), and evacetrapib (LY2484595, Eli Lilly), were announced to be failed to reduce CVD accidence although significantly elevating plasma HDL-C levels.

2.5 Scavenger receptor class B type I (SR-BI)

As the last step in RCT, SR-BI has been shown to function as another HDL receptor that mediates selective cholesterol uptake in the liver. SR-BI knockout mice remarkably elevate HDL-C levels but paradoxically increase atherosclerosis [28]. Some studies also reported that variant of SR-BI in which leucine replaces proline 376 (P376L) abrogates its ability to uptake HDL from plasma to the liver. Consequently, these patients have a profound HDL-related phenotype and an increased CVD risk [29].

3. HDL composition

Generally, HDL particles contain apolipoproteins, enzymes, charged lipids (phospholipids and free cholesterol) on the surface, and neutral lipids (TG and CE) in the core. The compositional complexity of HDL is further verified through the quantitative and qualitative proteome and lipidome assay, which carries more than 80 different proteins, over 200 lipid species, various microRNAs, as well as other bioactive molecules [30]. This physiological heterogeneity is further increased in the inflammatory conditions (e.g., CVD, diabetes mellitus, chronic kidney disease, and rheumatic diseases). The known functions associated with these components are diverse and span physiological roles far beyond the classical roles for HDL in lipid metabolism, suggesting that novel properties of HDL may exist. Therefore, it seems not reasonable to simply make HDL-C levels reflect the compositions and functions of HDL particles and predict the risk of CVD.

3.1 Apolipoprotein A-I (apoA-I)

ApoA-I is the most abundant protein of HDL, which is synthesized in the liver and intestine and almost located in all HDL particles. Mature apoA-I is a 28-kDa protein that consists of 243 amino acids and contains 10 amphipathic helical domains. It has been found that apoA-I plays a variety of roles associated with HDL metabolism. One primary function of apoA-I is to interact with cellular surface transporters (ABCA1), mediate cholesterol efflux, and activate LCAT, which exerts the foundational effects in RCT process as described above [31, 32]. Human subjects with apoA-I deficiency and apoA-I-deficient mice fail to form mature HDL particles [33]. Liver-specific overexpression of apoA-I was found to increase apoA-I and HDL-C levels in plasma, thereby reducing atherosclerosis in hyperlipidemic mice [34, 35]. In addition, apoA-I enhances the proliferation of human endothelial progenitor cells (EPCs) and promotes angiogenesis through ATP synthase in cell surface [36]. ApoA-I restores neovascularization of the lymphatic system in tumor necrosis factor (TNF)-alpha-mediated inflammatory responses [37]. We also found that human apoA-I induces cyclooxygenase-2 (COX-2) expression and prostaglandin I-2 (PGI2) release in endothelial cells through ABCA1 [38]. ApoA-I inhibits the chemotaxis, adhesion, and activation of THP-1 monocytes induced by lipopolysaccharide (LPS) and improves HDL inflammatory index (HII) in plasma [39]. Furthermore, apoA-I displays anti-inflammatory effects in adipocytes and adipose tissues similar to their effects in other cell types [40].

3.2 Paraoxonase-1 (PON1)

PON1 is a HDL-associated lactonase, which could hydrolyze a wide variety of lactones, thiolactones, aryl esters, cyclic carbonates, and organophosphate

pesticides and prevent LDL oxidation [41, 42]. Decreased PON1 activity is a risk factor for CVD development independently of HDL-C levels [43]. PON1 reduces oxidative stress, inhibits cholesterol synthesis, and promotes cholesterol efflux in macrophages [44, 45]. Low PON1 activity is associated with many inflammatory diseases, including diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and renal diseases [46]. In the presence of PON1, lipid hydroperoxide is reduced, monocyte chemotactic protein 1 (MCP-1) production is inhibited, and atherosclerotic progression is attenuated [47]. Overexpression of PON1 inhibits atherosclerosis in mice with metabolic syndrome [48]. Additionally, it has been shown that PON1 can prevent the development of diabetes mellitus in mice through its anti-oxidative properties, suggesting a possible role of PON1 in stimulating insulin biosynthesis in islet beta cells [49].

3.3 Phospholipids in HDL

Besides free cholesterol, TG, and CE, there are many kinds of phospholipids in HDL molecules, mainly including ceramide, sphingomyelin, and sphingosine-1-phosphate (S1P) [50]. These phospholipids are located 0n the surface monolayer of HDL together with free cholesterol and apolipoproteins. Ceramide mediates an inflammatory response induced by cytokines or oxidized LDL (ox-LDL), which upregulates the expression of adhesion molecules, increases the adhesion and migration of monocytes, and subsequently promotes the initiation and progression of CVD [51]. Sphingomyelin regulates cholesterol efflux from peripheral cells, which is considered to possess an inverse relationship with CVD [52].

S1P is a bioactive lipid mediator generated by the phosphorylation of sphingosine via sphingosine kinases (SphK) 1 and SphK2, which plays variously biological and pathophysiological roles through three members of G protein-coupled S1P receptors (S1P1, S1P2, and S1P3) [53]. These S1P receptors are differentially expressed, regulating proliferation, migration, adhesion, and inflammation in endothelial cells, smooth muscle cells, and macrophages, all of which play key roles in the development of CVD [54, 55]. HDL-associated S1P limits endothelial inflammation induced by TNF-alpha, including adhesion molecule abundance, monocyte-endothelial adhesion, and endothelial barrier permeability [56, 57]. S1P elevates endothelial nitric oxide synthase (eNOS) activity and promotes nitric oxide (NO) release in endothelial cells [58]. S1P induces endothelial cell migration and proliferation, prevents apoptosis and inflammation, improves vascular relaxation, and preserves endothelial barrier function [55, 59, 60]. Some studies showed that reduced HDL-S1P content contributes to HDL dysfunction in CVD patients, including induction of eNOS activation in endothelial cells and promotion of vasodilatory potential in precontracted arteries. These decreased HDL functions could be efficiently improved by loading additional S1P to HDL both *in vitro* and *in vivo* [61]. In addition, exogenously administrated S1P accelerates neovascularization and blood flow recovery in ischemic limbs, suggesting its usefulness for angiogenic therapy. Furthermore, S1P was also shown to regulate VSMC proliferation and migration and to manipulate vascular tension via G protein-coupled receptors [62].

S1P1 is mainly expressed in endothelial cells, which mediates vascular maturation and maintains vascular integrity by contributing to eNOS activation, inhibiting vascular permeability and inducing endothelial cell chemotaxis via Gi-coupled mechanisms [55]. By contrast, S1P2 is expressed in VSMCs and some types of tumor cells in high levels, which inhibits cell migration via the G(12/13)-and Rho-dependent mechanism [55]. S1P3 is also primarily expressed in endothelial cells and mediates chemotaxis and vasorelaxation through a NO-dependent manner, which

plays protective roles for vascular integrity [55]. These results provide evidence for S1P receptor subtype-specific pharmacological intervention as a novel therapeutic approach to CVD [63].

3.4 MicroRNAs (miRNAs) in HDL

miRNAs are small noncoding RNAs that suppress gene expression through post-transcriptional regulation of mRNA stability. Extracellular miRNAs likely serve as the cellular messages, which are transported between cells in an endocrine form of intercellular communication via circulation. In the blood vessels, these transferring miRNAs modulate atherosclerosis and angiogenesis, and in the heart, they modulate ischemic/reperfusion (I/R) injuries, myocardial infarction, and heart failure. In plasma, they are protected from circulating ribonucleases through the association with lipoproteins [64]. Especially, HDL is reported to be the major carrier of miRNAs in plasma. Furthermore, HDL exhibits an independent miRNA profile distinct from that of plasma through the micro-transcriptome assay, which might notably influence the biological functions of HDL [65].

HDL transports endogenous miRNAs and delivers them to recipient cells with functional targeting capabilities. Cellular export of miRNAs to HDL is regulated by neutral sphingomyelinase. Injecting reconstituted HDL (rHDL) into mice retrieves distinct miRNA profiles from normal and atherogenic animal models. Furthermore, HDL-mediated delivery of miRNAs to recipient cells was demonstrated to be dependent on SR-BI. The human HDL-miRNA profiles in healthy subjects are significantly different from those of familial hypercholesterolemia subjects. Notably, HDL-miRNAs from atherosclerotic subjects induce differential gene expression [66, 67]. Collectively, these observations indicated that HDL participates in a mechanism of intercellular communication through the delivery of miRNAs.

Some studies reported that the contents of miR-486 and miR-92a in HDL are reduced in vulnerable CVD patients [68]. HDL-associated miR-223 levels are decreased after high-protein diet-induced weight loss in overweight and obese males [69]. Intestinal lymphatic HDL-associated miR-223 is reduced during insulin resistance and is restored by niacin in rats [70]. Furthermore, HDL-transferred miR-223 inhibits intercellular adhesion molecule-1 (ICAM-1) expression in endothelial cells [71].

4. HDL functions beyond RCT

HDL exerts diverse biological functions besides removing cholesterol from peripheral cells through RCT, which have attracted considerable attentions.

4.1 Endothelial cell protections of HDL

Endothelial cells play fundamental roles in regulating vascular functions [72, 73]. Many risk factors for atherosclerosis (e.g., hypercholesterolemia, hypertension, and hyperglycemia) induce the inflammation and apoptosis in endothelial cells and initiate the pathogenesis of atherosclerosis [74]. Therefore, improving endothelial dysfunction is a potential target for preventing and treating CVD. HDL could inhibit cytokine-induced expression of vascular cell adhesion molecule-1 (VCAM-1) and ICAM-1 in human umbilical vein endothelial cells (HUVECs) and reduce the adhesion of monocytes to endothelial cells [75]. Moreover, HDL induces endothelial repair by enhancing eNOS activity and increasing NO production through the SR-BI and ABCG1 pathways [76, 77]. HDL also improves vascular

health by reducing apoptosis and promotes proliferation and migration in endothelial cells, which are crucial for neovascularization after vascular injuries [78].

4.2 HDL functions on vascular smooth muscle cells (VSMCs)

Many stress factors could induce VSMCs shifting from a contractile phenotype to a synthetic phenotype, and consequently the activated VSMCs proliferate and migrate from the medial layer of vessels into the intima which results in neointimal hyperplasia and artery stenosis [79, 80]. HDL counterbalances the pro-inflammatory effects of ox-LDL by inhibiting intracellular reactive oxygen species (ROS) release and subsequent nuclear factor kappa-B (NF-κB) activation in VSMCs [81]. HDL also downregulates the production of fibroblast growth factor (FGF) and represses the proliferation of VSMCs triggered by ox-LDL [82]. HDL suppresses the expression of chemokines (CCL2, CCL5, CX3CL1, CCR2, and CX3CR1) and the proliferation of VSMCs induced by TNF-alpha via the SR-BI pathway [7]. In addition, HDL-associated alpha-antitrypsin (AAT) inhibits extracellular matrix degradation, cell detachment, and apoptosis triggered by elastase in human VSMCs [83].

4.3 HDL against inflammation

HDL plays an important role against inflammatory responses [84, 85]. HDL is able to bind and neutralize LPS as well as to facilitate LPS release from the surface of macrophages, which inhibits macrophage activation and cytokine release [85–87]. HDL-bound LPS does not interact with the cellular membrane receptors in macrophages, thereby decreasing the uptake of LPS by macrophages. And apoA-I is identified as the LPS-binding molecule in HDL [88]. In rat models of LPS-mediated sepsis, infusion of rHDL significantly reduces cytokine release, organ injuries, and animal mortality [89]. In addition, elevation of plasma HDL-C levels in transgenic mice by overexpressing apoA-I protects against septic shock and death caused by LPS and severe bacterial infection [90]. Similarly, low levels of HDL-C increase the mortality in patients with sepsis/septic shock [91]. Systemic administration of rHDL blunts the deleterious effects of LPS caused by small doses of intravenous LPS injection in human volunteers, such as attenuating cytokine release, correcting procoagulant state, and downregulating CD14 expression [92, 93]. Furthermore, HDL was shown to suppress cytokine and chemokine production, downregulate co-stimulatory molecules, and inhibit antigen presentation in macrophages and monocyte-derived dendritic cells [94].

4.4 Regulation of glucose metabolism by HDL

HDL may favorably regulate glucose metabolism. HDL promotes glycogen synthesis in skeletal muscle myocytes via SR-BI and stimulates glucose uptake by adipocytes [95]. HDL and apoA-I stimulate glucose uptake by skeletal muscle myocytes via increasing adenosine monophosphate-activated protein kinase (AMPK) activity [96]. HDL also enhances insulin secretion by pancreatic beta cells, which requires ABCA1-mediated cholesterol efflux as well as SR-BI expression [97]. In patients with type 2 diabetes mellitus (T2DM), intravenously injecting rHDL increases plasma insulin levels and decreases glucose concentrations *in vivo* [98].

4.5 HDL and cancer

Epidemiological studies showed that CVD and cancer possess various similarities and possible interactions, including a number of common risk factors (e.g.,

smoking, obesity, and diabetes mellitus) and a shared biology [99]. Low HDL-C levels might be a prognostic factor for biliary tract cancer, prostate cancer, colon cancer, breast cancer, and gastric cancer [100, 101]. *In vitro* studies also demonstrated that native HDL could inhibit the migration and invasion of breast cancer cells [102, 103]. In addition, HDL could repress the adhesion of breast cancer cells to endothelial cells that mitigate the metastasis of breast cancer and reduce cancer growth through inhibiting tumor angiogenesis [104, 105].

5. Dysfunctional HDL in systemic inflammation

The potent atheroprotective effects of HDL originate from its unique composition and structure. If the composition or structure of HDL is altered in the setting of systemic inflammation (e.g., CVD and diabetes mellitus), it may lose its protective effects and even acquire deleterious functions, which is called dysfunctional HDL [106, 107]. Moreover, changes of HDL functions in systemic inflammation can also be the results of chemical modifications of HDL components without changing its composition. The most common modifications of HDL are oxidation and glycation of its proteins or lipids [9, 108]. Therefore, understanding the features of dysfunctional HDL might lead to a new diagnostic and therapeutic approach to CVD.

5.1 Dysfunctional HDL in CVD

In the early phase of acute myocardial infarction, the pro-inflammatory HDL particles display remarkable alterations, including increased levels of lysophosphatidylcholine (LysoPC), phosphatidic acid (PA), ceruloplasmin, and serum amyloid A (SAA); decreased amounts of apoA-I, PON1, and platelet-activating factor acetylhydrolase (PAF-AH); and reduced abilities of cholesterol efflux and anti-oxidative activity, which are implicated in the impaired functions of HDL [109, 110].

Myeloperoxidase (MPO) is released to plasma from monocytes and neutrophils in CVD, which uses hydrogen peroxide to generate hypochlorous acid (HClO) and subsequently causes oxidative modifications of lipids and proteins of lipoproteins, rendering HDL dysfunctions [111, 112]. Some studies found that MPO-dependent oxidation of HDL reduces the binding affinity of HDL to receptors and impairs its ability to stimulate cholesterol efflux from foam cells [113, 114]. Meanwhile, oxidized HDL (ox-HDL) can induce ROS production and upregulate the expression of pro-inflammatory and pro-thrombotic genes, such as TNF-alpha, matrix metalloproteinase-2/-9 (MMP-2/-9), COX-2, and plasminogen activator inhibitor-1 (PAI-1), which elevates CVD risk [115–117]. In addition, ox-HDL is dysfunctional in inducing NO production and promoting endothelial repair *in vitro* and reendothelialization of injured carotid arteries *in vivo* [118, 119]. And ox-HDL also promotes VSMC proliferation and migration by triggering intercellular ROS production [120]. Furthermore, ox-HDL has an elevated capability to induce the proliferation, migration, and invasion of breast cancer cells, thereby promoting the metastasis of breast cancer [103, 121].

5.2 Abnormal HDL in diabetes mellitus

HDL could be deficient in T2DM conditions, because of enrichment of TG, depletion of CE, and glycation of apoA-I and HDL-associated enzymes. These changes impair the structure and function of HDL, reduce receptor-mediated cholesterol efflux, and increase CVD risk [122, 123]. Glycation of HDL *in vitro* reduces its capacity to mediate cholesterol efflux from THP-1 macrophages, and incubation

with glycation inhibitors (metformin and aminoguanidine) restores HDL-mediated cholesterol efflux [124, 125]. HDL from diabetic subjects reduces the abilities of anti-oxidation and anti-apoptosis as well as the capacities to mediate cholesterol efflux from THP-1 macrophages, which result from depleting HDL-associated apoA-I level and PON1 activity and elevating SAA concentration [126–128]. Both glycated HDL *in vitro* and diabetic HDL lose their protective effects on inhibition of cytokine release against LPS in macrophages [129]. Moreover, diabetic HDL is less effective to stimulate NO production, to promote proliferation and migration in endothelial cells by downregulating SR-BI, and to improve endothelium-dependent vasodilation and endothelial repairment [130, 131]. In addition, HDL from diabetic patients leads to abnormal actions on breast cancer cell adhesion to endothelial cells and extracellular matrix, thereby promoting the metastasis of breast cancer [132]. HDL from T2DM patients carries a higher level of S1P, which could be partly responsible for the abnormal functions of diabetic HDL [133]. CETP activity is elevated in diabetic patients compared to healthy subjects, resulting in changed HDL remodeling and accelerated HDL clearance [134]. ApoA-I is glycated in T2DM patients *in vivo* and by glucose or methylglyoxal *in vitro*, and such glycation may impair its anti-inflammatory effects in endothelial cells [135, 136]. Some specific lysine (K) residues of apoA-I (K12, K23, K40, K96, K106, K107, and K238) are susceptible to be glycated either *in vitro* or *in vivo*, which alter the conformation of apoA-I and consequently impair the anti-inflammatory effects of apoA-I in diabetic conditions [137].

Plasma levels of ox-HDL in T2DM patients were reported to be higher than those in healthy individuals [138]. It was found that ox-HDL is independently and positively correlated with fasting glucose levels, suggesting that high glucose levels may also contribute to HDL oxidation [139]. Glycated HDL is more susceptible to oxidation *in vitro* as shown by an increase in lipid peroxidation products and thiobarbituric acid-reactive substances (TBARS) following incubation of HDL with glucose.

6. HDL particles (HDL-P)

HDL comprises a heterogeneous group of discoid and spherical particles (7–12 nm in diameter) that differ in density, size, and electrophoretic mobility [30]. As whether plasma HDL-C levels could really reflect the whole HDL compositions and whether HDL-C is still a good predictor for CVD are questioned; quantitative measurements of HDL particles (HDL-P) might be more valuable and meaningful than HDL-C [140]. In addition, HDL is a complex carrier for many kinds of proteins, lipids, and other biochemical materials in plasma as mentioned above, which might make it to be the natural endogenous nanoparticles that deliver cargoes targeted to recipient cells.

6.1 HDL subclasses

Distinct content in proteins and lipids results in various HDL subclasses, each characterized by differences in shape, density, size, and charge. Broadly, HDL can be distinguished into two subfractions by density: HDL2 and HDL3. HDL2 is larger, less dense, and strongly associated with apoA-I, which carries the majority of cholesterol reflected in HDL-C measurements. Unlike HDL2, HDL3 carries proteins that prevent oxidative stress and receive cholesterol from RCT through ABCA1. HDL3 cholesterol is well approximated by the sum of small and medium HDL-P concentration, whereas HDL2 cholesterol correlates strongly with large HDL-P concentration. By the action of LCAT, small HDL3 is progressively transformed to CE-enriched HDL2. CETP mediates the hetero-transfer of TG and CE between

HDL2a- and TG-rich lipoproteins, resulting in the formation of HDL2b subspecies. These latter particles are then transformed back to HDL3c by hydrolysis of TG and phospholipids as a result of the combined action of phospholipid transfer protein (PLTP), hepatic lipase (HL), and CETP [141, 142].

6.2 HDL-P measurement

Experimental studies pointed out that the widely used measurements of HDL-C levels may have obvious limitations, and the quantitative evaluation of HDL-P might be a more robust biomarker for assessing HDL functions and predicting CVD risk [11, 140]. A number of epidemiological and clinical trials, including the Heart Protection Study (HPS) [143], the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) [144], and the Multi-Ethnic Study of Atherosclerosis (MESA) [145], demonstrated that HDL-P is a stronger and more independent predictor of CVD risk than HDL-C. In JUPITER study, investigators evaluated the relationship of HDL-C and HDL-P in more than 10,000 subjects with CVD risk. JUPITER showed a significant inverse association between HDL-P and CVD risk. In contrast, HDL-C is not associated with CVD risk in statin-treated patients after adjustment for additional lipoprotein parameters [144]. MESA also found that HDL-P is a significant predictor of incident CVD events and carotid intima-media thickening (cIMT), even adjusting for HDL-C levels and other CVD confounders [145]. In addition, HDL-P is an independent predictor of major adverse cardiovascular events (MACE) among patients undergoing angiography [146]. Therefore, HDL-P might provide a more accurate and reliable measure of HDL than HDL-C.

6.3 HDL: nature's nanoparticles

Compared to the artificial nanocarriers (e.g., liposomes, micelles, inorganic, and polymeric nanoparticles), HDL-based drug delivery strategies have unique features that deliver drugs, peptides/proteins, nucleic acids, and imaging agents targeted to various organs more efficiently [147]. These attributes of HDL include ultrasmall size (8–12 nm), high tolerability in humans (up to 8 g of protein per infusion), long circulating half-life (12–24 h), and intrinsic targeting properties to specific recipient cells [148, 149]. A statin-loaded rHDL nanoparticle remarkably inhibits the inflammatory responses in atherosclerotic plaque [150]. Moreover, nanoparticle-labeled HDL might be used to evaluate the stability of atherosclerotic plaque through magnetic resonance imaging (MRI) after intraperitoneal application [151].

Furthermore, HDL is the natural anticancer drug delivery system for tumor imaging and treatment, which provides tumor-selective delivery of anticancer agents while reducing harmful off-target effects [152, 153]. Therefore, utilizing HDL nanoparticles would revolutionize the future strategy for the management of a broad range of cancers. Synthetic HDL nanoparticles could act synergistically and lessen the amount of mitotane/etoposide/cisplatin needed for anticancer efficacy in adrenocortical carcinoma [154]. The binding of anticancer drug valrubicin with rHDL increases the water solubility of valrubicin, which appears ideally suited for extended applications, including systemic cancer chemotherapy [155]. Artificial HDL nanoparticles using a gold nanoparticle induce B lymphoma cell apoptosis through SR-BI-mediated cholesterol starvation and selectively inhibit B-cell lymphoma growth in mice [156]. In addition, after delivering anti-angiogenic RNAi to endothelial cells, HDL strongly attenuates neovascularization *in vivo* and reduces tumor growth, which might be a potential treatment for cancer [157].

7. Apolipoprotein mimetic peptides

Synthetic peptides modeling the amphipathic helices in apoA-I and apolipoprotein E (apoE) show the similar antiatherogenic properties to native ones, including promoting cholesterol efflux, improving oxidative stress, and reducing inflammatory response.

7.1 ApoA-I mimetic peptides

Studies found that the interaction between apoA-I and ABCA1 is not sequence-specific and instead the amphipathic helices of apoA-I are identified as the key structural motifs [158]. To further understand these helices, a model of 18-amino acid peptide (18A) was developed, which is not identical in sequence to any of the individual helices of apoA-I [159]. 18A is referred to as 2F because it contains two phenylalanine (F) residues, which could solubilize phospholipids and activate LCAT. Many peptides were further designed on the basis of 2F to enhance the biological activities of the peptides [160, 161]. Among them, 4F, containing four F residues, is the most well-studied peptide, which significantly reduces atherosclerotic lesion in apoE knockout and LDL-R null mice [162, 163]. The ability of 4F to promote cholesterol efflux was also noted, although it is not as effective as lipid-free apoA-I [164]. L-4F, synthesized with natural L-amino acids, is effective but not stable when administered orally, presumably due to its susceptibility to proteolysis in the intestine [162]. This problem was circumvented by fabrication of D-4F with D-amino acids, which displays the similar biological properties to L-4F and exerts significant antiatherogenic effects upon oral administration [162]. D-4F protects endothelial cells against ox-LDL-induced injury by antagonizing the downregulation of pigment epithelium-derived factor (PEDF) [105]. We also found that D-4F alleviates ox-LDL-induced oxidative stress and promotes endothelial repair through the eNOS/HO-1 pathway [165]. Besides, D-4F accelerates vasodilatation and restrains atherosclerosis by regulating phospholipid metabolites and decreasing plasma LysoPC in LDL-R null mice [166]. Furthermore, D-4F decreases the myocardial infarction area in hyperglycemia mice through promoting NO release and decreasing ROS generation in endothelial cells [167]. Metabolomic analysis showed that D-4F alleviates ox-LDL-induced oxidative stress and abnormal glycolysis in endothelial cells [168].

In addition, 6F is also bioactive even made from L-amino acids and presented orally [169]. End-blocked 6F is more hydrophobic than 4F, more effectively activates LCAT, and is at least as effective in binding oxidized lipids [170, 171]. The 5A peptide possesses many functional attributes of native apoA-I including cholesterol efflux, inhibition of LDL oxidation, and suppression of inflammation [172]. Additionally, 5A reduces atherosclerosis and prevents the induction of asthma in mouse models [173, 174].

7.2 ApoE-mimetic peptides

ApoE is a multifunctional apolipoprotein that associates with VLDL, LDL, and subsets of HDL. It participates in the clearance of these lipoproteins from plasma, by serving as ligand for LDL-R and its family of related receptors. Like apoA-I, it is also active in RCT and has anti-inflammatory and anti-oxidative activities [175]. These properties are believed to contribute to the antiatherogenic functions of apoE. Mimetic peptides derived from apoE have been developed. AT1–5261 is an apoE-mimetic peptide containing 25 amino acids [176]. In the lipid-free state, ATI-5261 efficiently promotes ABCA1-mediated cholesterol efflux. When the peptide is

complexed with phospholipids, it is still capable of promoting cholesterol efflux in a partially ABCA1-dependent fashion [176].

7.3 Dual-domain peptides

The rationale for constructing the dual-domain peptide (Ac-hE18A-NH2) is that 18A promotes the association of lipid-free apoE ligand-binding sequence with lipoproteins. The peptide Ac-hE18A-NH2 lowers plasma cholesterol levels in hyperlipidemic mice [177, 178]. *In vitro* studies, Ac-hE18A-NH2 also decreases monocyte adhesion to endothelial cells, attenuates LPS-induced inflammatory responses in HUVECs, and reduces lipid hydroperoxides in LDL [178]. Compared to 4F, Ac-hE18A-NH2 peptide was also shown to promote cholesterol efflux, improve endothelial dysfunctions, and lower plasma lipid hydroperoxides [179]. 4F binds oxidized lipid with high affinity, and Ac-hE18A-NH2 rapidly reduces plasma cholesterol levels, including lowering VLDL and LDL levels [177].

8. Other therapeutics targeted to HDL

Besides the traditional drugs (e.g., statins, niacin, and PPARs agonists), there are some emerging molecules targeted to regulating HDL metabolism [180].

8.1 RVX-208 (apabetalone)

RVX-208 is a selective antagonist of the bromodomain of bromodomain and extra-terminal (BET), which induces apoA-I mRNA and protein expression through an epigenetic mechanism in hepatocytes *in vitro*, leading to elevated levels of plasma apoA-I and HDL-C *in vivo* [181–183]. RVX-208 selectively binds to BET bromodomains, competing for a site bound by the endogenous ligand (acetylated lysine) [184]. RVX-208 also increases HDL-C levels, decreases LDL-C contents, and reduces atherosclerotic plaque formation in hyperlipidemic apoE knockout mice [185]. Thus, RVX-208 might be a promising new approach for CVD treatment.

Microarray analysis found that RVX-208 upregulates many antiatherogenic gene expression and downregulates lots of pro-atherogenic gene expression *in vivo* [186]. RVX-208 reduces the vascular inflammation *in vitro* and in CVD patients by a BET-dependent epigenetic mechanism [187]. RVX-208 remarkably represses the expression of pro-inflammatory cytokines (VCAM-1, MCP-1, and IL-6) *in vitro* and *in vivo* [185]. RVX-208 also increases 10 lipid classes in plasma HDL fractions, delays oral glucose absorption and endogenous glucose production, and reduces peripheral glucose disposal, which may protect against T2DM development [188]. RVX-208 reduces the expression of complement factors either *in vitro* or in mice and in CVD patients [189]. RVX-208 counters the trans-differentiation and calcification of VSMCs [190]. RVX-208 lowers serum alkaline phosphatase levels and improves CVD risk [191]. RVX-208 favorably modulates the vulnerability of carotid artery plaque through ultrasonic measurement, which is related to an increase of HDL-P levels [192]. These results demonstrated that the antiatherogenic functions of RVX-208 occur via a combination of lipid profile changes, anti-inflammatory activities, as well as many other protective properties.

Recently, phase II trials showed that RVX-208 reduces MACE in treated patients, over and above that of apoA-I/HDL increasing action. This MACE reducing actions of RVX-208 is largely due to its novel anti-inflammatory actions [193, 194]. Currently, a phase III trial, BETonMACE, is ongoing to look for the effects of RVX-208 in CVD patients. Therefore, RVX-208 might act in multiple ways to inhibit atherosclerosis and would be an emerging option for CVD

management. However, we still need long-term phase III trial data to verify these effects on real-world CVD patients.

8.2 Liver X receptor (LXR) agonists

LXR agonists, as the key regulators of ABCA1/ABCG1 expression in macrophages, have been shown to promote cholesterol efflux in macrophages *in vitro*, raise HDL-C levels, and decrease atherosclerosis in LDL-R knockout mice [195, 196]. Studies have highlighted the primary antiatherogenic activity of LXR agonists on macrophages [197]. Unfortunately, the first generation of LXR compounds has been hampered by their capacity to promote the expression of lipogenic genes in the liver, which elevate TG levels and increase hepatic steatosis [198]. LXR activator, T091317, induces gene expression of Niemann-Pick C1/2 (NPC1/2) in macrophages, increases cholesterol content in the outer layer of macrophage membranes, and decreases atherosclerosis in mice [199]. A novel LXR agonist, ATI-111, also prevents atherosclotic plaque formation in mice [200]. LXR agonist (LXR-623) is associated with increased expression of ABCA1 and ABCG1, but adverse central nervous system-related effects are noted in more than half of patients, leading to termination of the study [201, 202]. Other agonists (AZ876 and GW3965) were also shown to reduce the progression of atherosclerotic lesions [203]. Interestingly, restricting LXR activation to the intestine might also result in an increase in intestinal HDL formation via ABCA1, without developing fatty liver [204]. An intestinal-specific LXR agonist, GW6340, promotes cholesterol efflux in macrophages and increases intestinal excretion of HDL-C [205]. Thus, LXR agonists may be a highly plausible and conceptually attractive target for the treatment of dyslipidemia and atherosclerosis, particularly if it can be accomplished with selective targeting to macrophage or the intestine.

8.3 Farnesoid X receptor (FXR) agonists

FXR is a bile acid-activated nuclear receptor that regulates cholesterol homeostasis and HDL metabolism [206]. Activation of FXR is reported to lead to both pro- and anti-atherosclerotic effects, because a major metabolic change caused by FXR agonists is a reduction of plasma HDL-C in LDL-R knockout mice [206, 207]. In addition, FXR agonists promote HDL-C excretion into feces in mice and monkeys [207]. Therefore, FXR agonists have received much attention as a potential therapeutic target, and different agonists (GW4064, 6ECDCA, FXR-450, and PX20606) have been generated as a strategy for regulating HDL metabolism [207, 208]. These observations will support further studies to investigate the potential roles of FXR activation on HDL regulation.

8.4 miRNA inhibitors

HDL is a major carrier of circulating miRNAs in plasma as mentioned above. Meanwhile, miRNAs have also emerged as the important regulators on HDL metabolism. Several studies demonstrated that miRNAs control the expression of a large number of genes associated with HDL metabolism, including ABCA1, ABCG1, and SR-BI [209, 210]. These findings strongly suggested that miRNAs regulate HDL biogenesis, cholesterol efflux, and uptake in the liver, thereby controlling the whole RCT process [211, 212].

miR-33 could repress the expression of ABCA1/ABCG1 proteins; however, knockout of miR-33 upregulates ABCA1/ABCG1 expression, promotes HDL-mediated cholesterol efflux, increases plasma HDL-C levels, and prevents the progression of atherosclerosis [213–215]. Besides raising HDL-C levels, inhibition of

miR-33 also lowers VLDL-TG contents in nonhuman primates [216]. Furthermore, anti-miR-33 therapy inhibits the gene expressions that enhance mitochondrial respiration and ATP production, promotes macrophage cholesterol efflux accompanying with ABCA1 upregulation, and reduces atherosclerosis [217]. In addition, miR33 inhibition overcomes the deleterious effects of atherosclerosis plaque progression in LDL-R knockout mice and diabetic mice [218, 219].

Additionally, inhibiting miR-144 could upregulate hepatic ABCA1 expression and increase HDL-C levels through the FXR-dependent pathway [220]. However, overexpression of miR-144 in the liver reduces ABCA1 expression, attenuates cholesterol efflux in macrophages, reduces HDL-C levels, and promotes atherosclerosis development [221]. An increase in miR-145 decreases ABCA1 expression and reduces plasma HDL-C levels and glucose-stimulated insulin secretion in islets. However, inhibiting miR-145 produces the opposite effects of increasing ABCA1 expression, promoting HDL biogenesis in the liver and improving glucose-stimulated insulin secretion in islets [222]. In mice, inhibition of miR-148a increases the hepatic expression of LDL-R and ABCA1, subsequently decreases plasma LDL-C concentrations, and elevates HDL-C levels, which may decrease LDL-C/HDL-C ratio and CVD risk [223]. Furthermore, miR-185, miR-96, and miR-223 may repress selective HDL-C uptake through inhibiting hepatic SR-BI, implying a novel mode of SR-BI regulation and an important role of miRNAs in modulating cholesterol metabolism [224]. Thus, these findings strongly supported the idea of developing miRNA inhibitors for the treatment of dyslipidemia and atherosclerosis [225].

9. Conclusions

As the failure of CEPT inhibitors on reducing CVD risk, the traditional concept of HDL against CVD from Framingham study has been challenged. Besides, abnormal HDL functions in the setting of systemic diseases also make HDL more confused to be understood. Consequently, whether HDL-C is still a good predictor for CVD and whether HDL could really provide valuable protections against CVD are questioned. HDL comprises a heterogeneous group of particles composed of various of bioactive components. The compositional complexity of HDL is almost hardly to be reflected by measuring cholesterol contents loading in HDL. Thus, quantifying HDL-P numbers and evaluating HDL functions might be the more meaningful markers for CVD prediction. Meanwhile, many emerging strategies targeted to regulate HDL metabolism and increase HDL-P levels were also attempted. Expectedly, more available measurement methods and therapeutic agents about HDL would arise in the near future.

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Conflict of interest

The author declares that there are no conflicts of interest.

Notes/thanks/other declarations

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Appendices and nomenclature

AAT	alpha-antitrypsin
ABCA1	ATP-binding cassette transporter A1
ABCG1	ATP-binding cassette transporter G1
AMPK	adenosine monophosphate-activated protein kinase
apoA-I	apolipoprotein A-I
apoB	apolipoprotein B
BET	bromodomain and extra-terminal
CE	cholesteryl esters
CETP	cholesterol ester transfer protein
cIMT	carotid intima-media thickening
COX-2	cyclooxygenase-2
CVD	cardiovascular disease
eNOS	endothelial nitric oxide synthase
EPCs	endothelial progenitor cells
FGF	fibroblast growth factor
FXR	Farnesoid X receptor
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HDL-P	HDL particles
HII	HDL inflammatory index
HL	hepatic lipase
HOCl	hypochlorous acid
HUVECs	human umbilical vein endothelial cells
ICAM-1	intercellular adhesion molecule-1
I/R	ischemic/reperfusion
LCAT	lecithin cholesterol acyltransferase
LDL	low-density lipoprotein
LDL-R	low-density lipoprotein receptor
LPS	lipopolysaccharide
LXR	liver X receptor
LysoPC	lysophosphatidylcholine
MACE	major adverse cardiovascular events
miRNAs	microRNAs
MMP	metalloproteinases
MPO	myeloperoxidase
NF-κB	nuclear factor kappa-B
NO	nitric oxide
ox-HDL	oxidized HDL
ox-LDL	oxidized LDL
PA	phosphatidic acid
PAF-AH	platelet-activating factor acetylhydrolase
PAI-1	plasminogen activator inhibitor-1
PEDF	pigment epithelium-derived factor
PGI2	prostaglandin I-2

PLTP	phospholipid transfer protein
PON1	paraoxonase-1
RCT	reverse cholesterol transport
rHDL	reconstituted HDL
ROS	reactive oxygen species
S1P	sphingosine-1-phosphate
SAA	serum amyloid A
SR-BI	scavenger receptor class B type I
SM	sphingomyelin
SphK	sphingosine kinases
T2DM	type 2 diabetes mellitus
TBARS	thiobarbituric acid-reactive substances
TG	triglycerides
TNF-alpha	tumor necrosis factor-alpha
VCAM-1	vascular cell adhesion molecule-1
VSMCs	vascular smooth muscle cells

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