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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 incidence 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 on 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- α , 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 administered 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- κ B) 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- α 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, AT1-5261 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 atherosclerotic 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- κ B	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
PGI ₂	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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References

- [1] Gordon T, Castelli WP, Hjortland MC. High density lipoprotein as a protective factor against coronary heart disease. The Framingham study. *The American Journal of Medicine*. 1977;**62**:707-714. DOI: 10.1016/0002-9343(77)90874-9
- [2] Gotto AM, Brinton EA. Assessing low levels of high-density lipoprotein cholesterol as a risk factor in coronary heart disease: A working group report and update. *Journal of the American College of Cardiology*. 2004;**43**:717-724. DOI: 10.1016/j.jacc.2003.08.061
- [3] Gordon DJ, Probstfield JL, Garrison RJ. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation*. 1989;**79**:8-15. DOI: 10.1161/01.cir.79.1.8
- [4] Barter PJ, Caulfield M, Eriksson M. Effects of torcetrapib in patients at high risk for coronary events. *The New England Journal of Medicine*. 2007;**357**:2109-2122. DOI: 10.1056/NEJMoa0706628
- [5] Ballantyne CM, Miller M, Niesor EJ. Effect of dalcetrapib plus pravastatin on lipoprotein metabolism and high-density lipoprotein composition and function in dyslipidemic patients: Results of a phase IIb dose-ranging study. *American Heart Journal*. 2012;**163**: 515-521. DOI: 10.1016/j.ahj.2011.11.017
- [6] Joy TR. Novel HDL-based therapeutic agents. *Pharmacology & Therapeutics*. 2012;**135**:18-30. DOI: 10.1016/j.pharmthera.2012.03.004
- [7] van der Vorst EP, Vanags LZ, Dunn LL. High-density lipoproteins suppress chemokine expression and proliferation in human vascular smooth muscle cells. *FASEB Journal*. 2013;**27**:1413-1425. DOI: 10.1096/fj.12-212753
- [8] Rye KA, Barter PJ. Cardioprotective functions of HDLs. *Journal of Lipid Research*. 2014;**55**:168-179. DOI: 10.1194/jlr.R039297
- [9] Rosenson RS, Brewer HB Jr, Ansell BJ. Dysfunctional HDL and atherosclerotic cardiovascular disease. *Nature Reviews. Cardiology*. 2016;**13**:48-60. DOI: 10.1038/nrcardio.2015.124
- [10] Miller GJ, Miller NE. Plasma-high-density-lipoprotein concentration and development of ischaemic heart-disease. *Lancet*. 1975;**1**:16-19. DOI: 10.1016/s0140-6736(75)92376-4
- [11] Khera AV, Demler OV, Adelman SJ. Cholesterol efflux capacity, high-density lipoprotein particle number, and incident cardiovascular events: An analysis from the JUPITER trial (justification for the use of statins in prevention: An intervention trial evaluating rosuvastatin). *Circulation*. 2017;**135**:2494-2504. DOI: 10.1161/CIRCULATIONAHA.116.025678
- [12] Brooks-Wilson A, Marcil M, Clee SM. Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency. *Nature Genetics*. 1999;**22**:336-345. DOI: 10.1038/11905
- [13] Tall AR, Yvan-Charvet L, Terasaka N. HDL, ABC transporters, and cholesterol efflux: Implications for the treatment of atherosclerosis. *Cell Metabolism*. 2008;**7**:365-375. DOI: 10.1016/j.cmet.2008.03.001
- [14] Lee JY, Parks JS. ATP-binding cassette transporter AI and its role in HDL formation. *Current Opinion in Lipidology*. 2005;**16**:19-25. DOI: 10.1097/00041433-200502000-00005
- [15] Tang C, Liu Y, Kessler PS. The macrophage cholesterol exporter ABCA1 functions as an anti-inflammatory receptor. *The Journal of*

Biological Chemistry. 2009;**284**:32336-32343. DOI: 10.1074/jbc.M109.047472

[16] Wang N, Lan D, Chen W. ATP-binding cassette transporters G1 and G4 mediate cellular cholesterol efflux to high-density lipoproteins. Proceedings of the National Academy of Sciences of the United States of America. 2004;**101**:9774-9779. DOI: 10.1073/pnas.0403506101

[17] Kobayashi A, Takanezawa Y, Hirata T. Efflux of sphingomyelin, cholesterol, and phosphatidylcholine by ABCG1. Journal of Lipid Research. 2006;**47**:1791-1802. DOI: 10.1194/jlr.M500546-JLR200

[18] Czarnecka H, Yokoyama S. Regulation of cellular cholesterol efflux by lecithin: Cholesterol acyltransferase reaction through nonspecific lipid exchange. Journal of Biological Chemistry. 1996;**271**:2023-2028. DOI: 10.1074/jbc.271.4.2023

[19] Guerin M, Dachet C, Goulinet S. Familial lecithin:cholesterol acyltransferase deficiency: Molecular analysis of a compound heterozygote: LCAT (Arg147→Trp) and LCAT (Tyr171→stop). Atherosclerosis. 1997;**131**:85-95. DOI: 10.1016/s0021-9150(97)06079-6

[20] Francone OL, Haghpassand M, Bennett JA. Expression of human lecithin:cholesterol acyltransferase in transgenic mice: Effects on cholesterol efflux, esterification, and transport. Journal of Lipid Research. 1997;**38**:813-822. DOI: 10.1089/jlr.1997.17.229

[21] Barter PJ, Brewer HB Jr, Chapman MJ. Cholesteryl ester transfer protein: A novel target for raising HDL and inhibiting atherosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology. 2003;**23**:160-167. DOI: 10.1161/01.atv.0000054658.91146.64

[22] Inazu A, Brown ML, Hesler CB. Increased high-density lipoprotein

levels caused by a common cholesteryl-ester transfer protein gene mutation. The New England Journal of Medicine. 1990;**323**:1234-1238. DOI: 10.1056/NEJM199011013231803

[23] Ishigami M, Yamashita S, Sakai N. Large and cholesteryl ester-rich high-density lipoproteins in cholesteryl ester transfer protein (CETP) deficiency cannot protect macrophages from cholesterol accumulation induced by acetylated low-density lipoproteins. Journal of Biochemistry. 1994;**116**:257-262. DOI: 10.1093/oxfordjournals.jbchem.a124516

[24] Matsuura F, Wang N, Chen W. HDL from CETP-deficient subjects shows enhanced ability to promote cholesterol efflux from macrophages in an apoE- and ABCG1-dependent pathway. The Journal of Clinical Investigation. 2006;**116**:1435-1442. DOI: 10.1172/JCI27602

[25] de Grooth GJ, Kuivenhoven JA, Stalenhoef AF. Efficacy and safety of a novel cholesteryl ester transfer protein inhibitor, JTT-705, in humans: A randomized phase II dose-response study. Circulation. 2002;**105**:2159-2165. DOI: 10.1161/01.cir.0000015857.31889.7b

[26] Brousseau ME, Schaefer EJ, Wolfe ML. Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol. The New England Journal of Medicine. 2004;**350**:1505-1515. DOI: 10.1056/NEJMoa031766

[27] Schwartz GG, Olsson AG, Ballantyne CM. Rationale and design of the dal-OUTCOMES trial: Efficacy and safety of dalcetrapib in patients with recent acute coronary syndrome. American Heart Journal. 2009;**158**:896-901. DOI: 10.1016/j.ahj.2009.09.017

[28] Acton S, Rigotti A, Landschulz KT. Identification of scavenger receptor SR-BI as a high density lipoprotein

receptor. *Science*. 1996;**271**:518-520.
DOI: 10.1126/science.271.5248.518

[29] Zanoni P, Khetarpal SA, Larach DB. Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease. *Science*. 2016;**351**:1166-1171. DOI: 10.1126/science.aad3517

[30] Annema W, von Eckardstein A. High-density lipoproteins. Multi-functional but vulnerable protections from atherosclerosis. *Circulation Journal*. 2013;**77**:2432-2448. DOI: DN/JSTJSTAGE/circj/CJ-13-1025

[31] Zannis VI, Chroni A, Krieger M. Role of apoA-I, ABCA1, LCAT, and SR-BI in the biogenesis of HDL. *Journal of Molecular Medicine (Berlin, Germany)*. 2006;**84**:276-294. DOI: 10.1007/s00109-005-0030-4

[32] Gelissen IC, Harris M, Rye KA. ABCA1 and ABCG1 synergize to mediate cholesterol export to apoA-I. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2006;**26**:534-540. DOI: 10.1161/01.ATV.0000200082.58536.e1

[33] Williamson R, Lee D, Hagaman J. Marked reduction of high density lipoprotein cholesterol in mice genetically modified to lack apolipoprotein A-I. *Proceedings of the National Academy of Sciences of the United States of America*. 1992;**89**:7134-7138. DOI: 10.1073/pnas.89.15.7134

[34] Rubin EM, Krauss RM, Spangler EA. Inhibition of early atherogenesis in transgenic mice by human apolipoprotein AI. *Nature*. 1991;**353**:265-267. DOI: 10.1038/353265a0

[35] Plump AS, Scott CJ, Breslow JL. Human apolipoprotein A-I gene expression increases high density lipoprotein and suppresses atherosclerosis in the apolipoprotein E-deficient mouse. *Proceedings of the*

National Academy of Sciences of the United States of America. 1994;**91**:9607-9611. DOI: 10.1073/pnas.91.20.9607

[36] Gonzalez-Pecchi V, Valdes S, Pons V. Apolipoprotein A-I enhances proliferation of human endothelial progenitor cells and promotes angiogenesis through the cell surface ATP synthase. *Microvascular Research*. 2015;**98**:9-15. DOI: 10.1016/j.mvr.2014.11.003

[37] Bisoendial R, Tabet F, Tak PP. Apolipoprotein A-I limits the negative effect of tumor necrosis factor on lymphangiogenesis. *Arteriosclerosis, and Thrombosis, and Vascular Biology*. 2015;**35**:2443-2450. DOI: 10.1161/ATVBAHA.115.305777

[38] Liu D, Ji L, Tong X. Human apolipoprotein A-I induces cyclooxygenase-2 expression and prostaglandin I-2 release in endothelial cells through ATP-binding cassette transporter A1. *American Journal of Physiology Cell Physiology*. 2011;**301**:C739-C748. DOI: 10.1152/ajpcell.00055.2011

[39] Wang L, Chen WZ, Wu MP. Apolipoprotein A-I inhibits chemotaxis, adhesion, activation of THP-1 cells and improves the plasma HDL inflammatory index. *Cytokine*. 2010;**49**:194-200. DOI: 10.1016/j.cyto.2009.08.008

[40] Umemoto T, Han CY, Mitra P. Apolipoprotein AI and high-density lipoprotein have anti-inflammatory effects on adipocytes via cholesterol transporters: ATP-binding cassette A-1, ATP-binding cassette G-1, and scavenger receptor B-1. *Circulation Research*. 2013;**112**:1345-1354. DOI: 10.1161/CIRCRESAHA.111.300581

[41] Rajkovic MG, Rumora L, Barisic K. The paraoxonase 1, 2 and 3 in humans. *Biochemia Medica (Zagreb)*. 2011;**21**:122-130. DOI: 10.11613/bm.2011.020

- [42] Deakin SP, Bioletto S, Bochaton-Piallat ML. HDL-associated paraoxonase-1 can redistribute to cell membranes and influence sensitivity to oxidative stress. *Free Radical Biology & Medicine*. 2011;**50**:102-109. DOI: 10.1016/j.freeradbiomed.2010.09.002
- [43] Mackness B, Durrington P, McElduff P. Low paraoxonase activity predicts coronary events in the Caerphilly prospective study. *Circulation*. 2003;**107**:2775-2779. DOI: 10.1161/01.CIR.0000070954.00271.13
- [44] Aviram M, Rosenblat M. Paraoxonases 1, 2, and 3, oxidative stress, and macrophage foam cell formation during atherosclerosis development. *Free Radical Biology & Medicine*. 2004;**37**:1304-1316. DOI: 10.1016/j.freeradbiomed.2004.06.030
- [45] Berrougui H, Loued S, Khalil A. Purified human paraoxonase-1 interacts with plasma membrane lipid rafts and mediates cholesterol efflux from macrophages. *Free Radical Biology & Medicine*. 2012;**52**:1372-1381. DOI: 10.1016/j.freeradbiomed.2012.01.019
- [46] Goswami B, Tayal D, Gupta N. Paraoxonase: A multifaceted biomolecule. *Clinica Chimica Acta*. 2009;**410**:1-12. DOI: 10.1016/j.cca.2009.09.025
- [47] Navab M, Imes SS, Hama SY. Monocyte transmigration induced by modification of low density lipoprotein in cocultures of human aortic wall cells is due to induction of monocyte chemotactic protein 1 synthesis and is abolished by high density lipoprotein. *Journal of Clinical Investigation*. 1991;**88**:2039-2046. DOI: 10.1172/JCI115532
- [48] Mackness B, Quarck R, Verreth W. Human paraoxonase-1 overexpression inhibits atherosclerosis in a mouse model of metabolic syndrome. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2006;**26**:1545-1550. DOI: 10.1161/01.ATV.0000222924.62641.aa
- [49] Rozenberg O, Shiner M, Aviram M. Paraoxonase 1 (PON1) attenuates diabetes development in mice through its antioxidative properties. *Free Radical Biology & Medicine*. 2008;**44**:1951-1959. DOI: 10.1016/j.freeradbiomed.2008.02.012
- [50] Hammad SM, Pierce JS, Soodavar F. Blood sphingolipidomics in healthy humans: Impact of sample collection methodology. *Journal of Lipid Research*. 2010;**51**:3074-3087. DOI: 10.1194/jlr.D008532
- [51] Chatterjee S. Sphingolipids in atherosclerosis and vascular biology. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1998;**18**:1523-1533. DOI: 10.1161/01.atv.18.10.1523
- [52] Martinez-Beamonte R, Lou-Bonafonte JM, Martinez-Gracia MV. Sphingomyelin in high-density lipoproteins: Structural role and biological function. *International Journal of Molecular Sciences*. 2013;**14**:7716-7741. DOI: 10.3390/ijms14047716
- [53] Hait NC, Oskeritzian CA, Paugh SW. Sphingosine kinases, sphingosine 1-phosphate, apoptosis and diseases. *Biochimica et Biophysica Acta*. 2006;**1758**:2016-2026. DOI: 10.1016/j.bbamem.2006.08.007
- [54] Argraves KM, Argraves WS. HDL serves as a S1P signaling platform mediating a multitude of cardiovascular effects. *Journal of Lipid Research*. 2007;**48**:2325-2333. DOI: 10.1194/jlr.R700011-JLR200
- [55] Kurano M, Yatomi Y. Sphingosine 1-phosphate and atherosclerosis. *Journal of Atherosclerosis and Thrombosis*. 2018;**25**:16-26. DOI: 10.5551/jat.RV17010
- [56] Ruiz M, Frej C, Holmer A. High-density lipoprotein-associated

- apolipoprotein M limits endothelial inflammation by delivering sphingosine-1-phosphate to the sphingosine-1-phosphate receptor 1. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2017;**37**:118-129. DOI: 10.1161/ATVBAHA.116.308435
- [57] Lucke S, Levkau B. Endothelial functions of sphingosine-1-phosphate. *Cellular Physiology and Biochemistry*. 2010;**26**:87-96. DOI: 10.1159/000315109
- [58] Igarashi J, Michel T. S1P and eNOS regulation. *Biochimica et Biophysica Acta*. 2008;**1781**:489-495. DOI: 10.1016/j.bbaliip.2008.06.008
- [59] Kimura T, Sato K, Kuwabara A. Sphingosine 1-phosphate may be a major component of plasma lipoproteins responsible for the cytoprotective actions in human umbilical vein endothelial cells. *Journal of Biological Chemistry*. 2001;**276**:31780-31785. DOI: 10.1074/jbc.M104353200
- [60] Kimura T, Sato K, Malchinkhuu E. High-density lipoprotein stimulates endothelial cell migration and survival through sphingosine 1-phosphate and its receptors. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2003;**23**:1283-1288. DOI: 10.1161/01.ATV.0000079011.67194.5A
- [61] Sattler K, Graler M, Keul P. Defects of high-density lipoproteins in coronary artery disease caused by low sphingosine-1-phosphate content: Correction by sphingosine-1-phosphate-loading. *The Journal of American College of Cardiology*. 2015;**66**:1470-1485. DOI: 10.1016/j.jacc.2015.07.057
- [62] Xing XQ, Li YL, Zhang YX. Sphingosine kinase 1/sphingosine 1-phosphate signalling pathway as a potential therapeutic target of pulmonary hypertension. *International Journal of Clinical and Experimental Medicine*. 2015;**8**:11930-11935
- [63] Takuwa Y, Okamoto Y, Yoshioka K. Sphingosine-1-phosphate signaling and biological activities in the cardiovascular system. *Biochimica et Biophysica Acta*. 2008;**1781**:483-488. DOI: 10.1016/j.bbaliip.2008.04.003
- [64] Das S, Halushka MK. Extracellular vesicle microRNA transfer in cardiovascular disease. *Cardiovascular Pathology*. 2015;**24**:199-206. DOI: 10.1016/j.carpath.2015.04.007
- [65] Desgagne V, Guerin R, Guay SP. Human high-density lipoprotein microtranscriptome is unique and suggests an extended role in lipid metabolism. *Epigenomics*. 2019;**11**:917-934. DOI: 10.2217/epi-2018-0161
- [66] Vickers KC, Palmisano BT, Shoucri BM. MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. *Nature Cell Biology*. 2011;**13**:423-433. DOI: 10.1038/ncb2210
- [67] Michell DL, Vickers KC. Lipoprotein carriers of microRNAs. *Biochimica et Biophysica Acta*. 2016;**1861**:2069-2074. DOI: 10.1016/j.bbaliip.2016.01.011
- [68] Niculescu LS, Simionescu N, Sanda GM. MiR-486 and miR-92a identified in circulating HDL discriminate between stable and vulnerable coronary artery disease patients. *PLoS One*. 2015;**10**:e0140958. DOI: 10.1371/journal.pone.0140958
- [69] Tabet F, Cuesta Torres LF, Ong KL. High-density lipoprotein-associated miR-223 is altered after diet-induced weight loss in overweight and obese males. *PLoS One*. 2016;**11**:e0151061. DOI: 10.1371/journal.pone.0151061
- [70] Mangat R, Borthwick F, Haase T. Intestinal lymphatic HDL miR-223 and ApoA-I are reduced during insulin resistance and restored with niacin. *FASEB Journal*. 2018;**32**:1602-1612. DOI: 10.1096/fj.201600298RR

- [71] Tabet F, Vickers KC, Cuesta Torres LF. HDL-transferred microRNA-223 regulates ICAM-1 expression in endothelial cells. *Nature Communications*. 2014;**5**:3292. DOI: 10.1038/ncomms4292
- [72] Lerman A, Zeiher AM. Endothelial function: Cardiac events. *Circulation*. 2005;**111**:363-368. DOI: 10.1161/01.CIR.0000153339.27064.14
- [73] Gimbrone MA Jr, Garcia-Cardena G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circulation Research*. 2016;**118**:620-636. DOI: 10.1161/CIRCRESAHA.115.306301
- [74] Higashi Y, Noma K, Yoshizumi M. Endothelial function and oxidative stress in cardiovascular diseases. *Circulation Journal*. 2009;**73**:411-418. DOI: JST.JSTAGE/circj/CJ-08-1102
- [75] Cockerill GW, Rye KA, Gamble JR. High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1995;**15**:1987-1994. DOI: 10.1161/01.atv.15.11.1987
- [76] Yuhanna IS, Zhu Y, Cox BE. High-density lipoprotein binding to scavenger receptor-BI activates endothelial nitric oxide synthase. *Nature Medicine*. 2001;**7**:853-857. DOI: 10.1038/89986
- [77] Terasaka N, Yu S, Yvan-Charvet L. ABCG1 and HDL protect against endothelial dysfunction in mice fed a high-cholesterol diet. *Journal of Clinical Investigation*. 2008;**118**:3701-3713. DOI: 10.1172/JCI35470
- [78] Riwanto M, Landmesser U. High density lipoproteins and endothelial functions: Mechanistic insights and alterations in cardiovascular disease. *Journal of Lipid Research*. 2013;**54**:3227-3243. DOI: 10.1194/jlr.R037762
- [79] Johnson JL. Emerging regulators of vascular smooth muscle cell function in the development and progression of atherosclerosis. *Cardiovascular Research*. 2014;**103**:452-460. DOI: 10.1093/cvr/cvu171
- [80] Chistiakov DA, Orekhov AN, Bobryshev YV. Vascular smooth muscle cell in atherosclerosis. *Acta Physiologica (Oxford, England)*. 2015;**214**:33-50. DOI: 10.1111/apha.12466
- [81] Robbesyn F, Garcia V, Auge N. HDL counterbalance the proinflammatory effect of oxidized LDL by inhibiting intracellular reactive oxygen species rise, proteasome activation, and subsequent NF-kappaB activation in smooth muscle cells. *FASEB Journal*. 2003;**17**:743-745. DOI: 10.1096/fj.02-0240fje
- [82] Cucina A, Scavo MP, Muzzioli L. High density lipoproteins downregulate basic fibroblast growth factor production and release in minimally oxidated-LDL treated smooth muscle cells. *Atherosclerosis*. 2006;**189**:303-309. DOI: 10.1016/j.atherosclerosis.2006.01.006
- [83] Ortiz-Munoz G, Houard X, Martin-Ventura JL. HDL antielastase activity prevents smooth muscle cell anoikis, a potential new antiatherogenic property. *FASEB Journal*. 2009;**23**:3129-3139. DOI: 10.1096/fj.08-127928
- [84] Murphy AJ, Woollard KJ, Hoang A. High-density lipoprotein reduces the human monocyte inflammatory response. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2008;**28**:2071-2077. DOI: 10.1161/ATVBAHA.108.168690
- [85] Wu A, Hinds CJ, Thiemermann C. High-density lipoproteins in sepsis and septic shock: Metabolism, actions, and therapeutic applications. *Shock*. 2004;**21**:210-221. DOI: 10.1097/01.shk.0000111661.09279.82
- [86] van Leeuwen HJ, van Beek AP, Dallinga-Thie GM. The role of high

density lipoprotein in sepsis. The Netherland Journal of Medicine. 2001;**59**:102-110. DOI: 10.1016/S0300-2977(01)00144-9

[87] Kitchens RL, Wolfbauer G, Albers JJ. Plasma lipoproteins promote the release of bacterial lipopolysaccharide from the monocyte cell surface. *Journal of Biological Chemistry*. 1999;**274**:34116-34122. DOI: 10.1074/jbc.274.48.34116

[88] Grunfeld C, Feingold KR. HDL and innate immunity: A tale of two apolipoproteins. *Journal of Lipid Research*. 2008;**49**:1605-1606. DOI: 10.1194/jlr.E800011-JLR200

[89] McDonald MC, Dhadly P, Cockerill GW. Reconstituted high-density lipoprotein attenuates organ injury and adhesion molecule expression in a rodent model of endotoxic shock. *Shock*. 2003;**20**:551-557. DOI: 10.1097/01.shk.0000097249.97298.a3

[90] Levine DM, Parker TS, Donnelly TM. In vivo protection against endotoxin by plasma high density lipoprotein. *Proceedings of the National Academy of Sciences of the United States of America*. 1993;**90**:12040-12044. DOI: 10.1073/pnas.90.24.12040

[91] Chien JY, Jerng JS, Yu CJ. Low serum level of high-density lipoprotein cholesterol is a poor prognostic factor for severe sepsis. *Critical Care Medicine*. 2005;**33**:1688-1693. DOI: 10.1097/01.ccm.0000171183.79525.6b

[92] Birjmohun RS, van Leuven SI, Levels JH. High-density lipoprotein attenuates inflammation and coagulation response on endotoxin challenge in humans. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2007;**27**:1153-1158. DOI: 10.1161/ATVBAHA.106.136325

[93] Pajkrt D, Doran JE, Koster F. Antiinflammatory effects of reconstituted high-density lipoprotein

during human endotoxemia. *The Journal of Experimental Medicine*. 1996;**184**:1601-1608. DOI: 10.1084/jem.184.5.1601

[94] Barter PJ, Nicholls S, Rye K-A. Antiinflammatory properties of HDL. *Circulation Research*. 2004;**95**:764-772. DOI: 10.1161/01.res.0000146094.59640.13

[95] Zhang Q, Zhang Y, Feng H. High density lipoprotein (HDL) promotes glucose uptake in adipocytes and glycogen synthesis in muscle cells. *PLoS One*. 2011;**6**:e23556. DOI: 10.1371/journal.pone.0023556

[96] Han R, Lai R, Ding Q. Apolipoprotein A-I stimulates AMP-activated protein kinase and improves glucose metabolism. *Diabetologia*. 2007;**50**:1960-1968. DOI: 10.1007/s00125-007-0752-7

[97] Fryirs MA, Barter PJ, Appavoo M. Effects of high-density lipoproteins on pancreatic beta-cell insulin secretion. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2010;**30**:1642-1648. DOI: 10.1161/ATVBAHA.110.207373

[98] Drew BG, Duffy SJ, Formosa MF. High-density lipoprotein modulates glucose metabolism in patients with type 2 diabetes mellitus. *Circulation*. 2009;**119**:2103-2111. DOI: 10.1161/CIRCULATIONAHA.108.843219

[99] Koene RJ, Prizment AE, Blaes A. Shared risk factors in cardiovascular disease and cancer. *Circulation*. 2016;**133**:1104-1114. DOI: 10.1161/CIRCULATIONAHA.115.020406

[100] Ganjali S, Ricciuti B, Pirro M. High-density lipoprotein components and functionality in cancer: State-of-the-art. *Trends in Endocrinology and Metabolism*. 2019;**30**:12-24. DOI: 10.1016/j.tem.2018.10.004

[101] Pirro M, Ricciuti B, Rader DJ. High density lipoprotein cholesterol and

cancer: Marker or causative? *Progress in Lipid Research*. 2018;**71**:54-69. DOI: 10.1016/j.plipres.2018.06.001

[102] Samadi S, Ghayour-Mobarhan M, Mohammadpour A. High-density lipoprotein functionality and breast cancer: A potential therapeutic target. *Journal of Cellular Biochemistry*. 2019;**120**:5756-5765. DOI: 10.1002/jcb.27862

[103] Pan B, Ren H, Ma Y. High-density lipoprotein of patients with type 2 diabetes mellitus elevates the capability of promoting migration and invasion of breast cancer cells. *International Journal of Cancer*. 2012;**131**:70-82. DOI: 10.1002/ijc.26341

[104] Huang X, He D, Ming J. High-density lipoprotein of patients with breast cancer complicated with type 2 diabetes mellitus promotes cancer cells adhesion to vascular endothelium via ICAM-1 and VCAM-1 upregulation. *Breast Cancer Research and Treatment*. 2016;**155**:441-455. DOI: 10.1007/s10549-016-3696-0

[105] Ding Y, Wang Y, Zhou J. Direct cytosolic siRNA delivery by reconstituted high density lipoprotein for target-specific therapy of tumor angiogenesis. *Biomaterials*. 2014;**35**:7214-7227. DOI: 10.1016/j.biomaterials.2014.05.009

[106] Ansell BJ, Fonarow GC, Fogelman AM. High-density lipoprotein: Is it always atheroprotective? *Current Atherosclerosis Reports*. 2006;**8**:405-411. DOI: 10.1007/s11883-006-0038-4

[107] Ansell BJ, Fonarow GC, Fogelman AM. The paradox of dysfunctional high-density lipoprotein. *Current Opinion in Lipidology*. 2007;**18**:427-434. DOI: 10.1097/MOL.0b013e3282364a17

[108] Smith JD. Dysfunctional HDL as a diagnostic and therapeutic target.

Arteriosclerosis, Thrombosis, and Vascular Biology. 2010;**30**:151-155. DOI: 10.1161/ATVBAHA.108.179226

[109] Huang Y, DiDonato JA, Levison BS. An abundant dysfunctional apolipoprotein A₁ in human atheroma. *Nature Medicine*. 2014;**20**:193-203. DOI: 10.1038/nm.3459

[110] Rached F, Lhomme M, Camont L. Defective functionality of small, dense HDL3 subpopulations in ST segment elevation myocardial infarction: Relevance of enrichment in lysophosphatidylcholine, phosphatidic acid and serum amyloid A. *Biochimica et Biophysica Acta*. 2015;**1851**:1254-1261. DOI: 10.1016/j.bbali.2015.05.007

[111] Zheng L, Nukuna B, Brennan ML. Apolipoprotein A-I is a selective target for myeloperoxidase-catalyzed oxidation and functional impairment in subjects with cardiovascular disease. *Journal of Clinical Investigation*. 2004;**114**:529-541. DOI: 10.1172/JCI21109

[112] Shao B, Oda MN, Oram JF. Myeloperoxidase: An oxidative pathway for generating dysfunctional high-density lipoprotein. *Chemical Research in Toxicology*. 2010;**23**:447-454. DOI: 10.1021/tx9003775

[113] Nagano Y, Arai H, Kita T. High density lipoprotein loses its effect to stimulate efflux of cholesterol from foam cells after oxidative modification. *Proceedings of the National Academy of Sciences of the United States of America*. 1991;**88**:6457-6461. DOI: 10.1073/pnas.88.15.6457

[114] Rifichi VA, Khachadurian AK. Oxidation of high density lipoproteins: Characterization and effects on cholesterol efflux from J774 macrophages. *Biochimica et Biophysica Acta*. 1996;**1299**:87-94. DOI: 10.1016/0005-2760(95)00198-0

- [115] Soumyarani VS, Jayakumari N. Oxidatively modified high density lipoprotein promotes inflammatory response in human monocytes-macrophages by enhanced production of ROS, TNF-alpha, MMP-9, and MMP-2. *Molecular and Cellular Biochemistry*. 2012;**366**:277-285. DOI: 10.1007/s11010-012-1306-y
- [116] Callegari E, Norata GD, Inoue H. Oxidized-HDL3 modulates the expression of Cox-2 in human endothelial cells. *International Journal of Molecular Medicine*. 2006;**18**:209-213. DOI: 10.3892/ijmm.18.1.209
- [117] Norata GD, Banfi C, Pirillo A. Oxidised-HDL3 induces the expression of PAI-1 in human endothelial cells. Role of p38MAPK activation and mRNA stabilization. *British Journal of Haematology*. 2004;**127**:97-104. DOI: 10.1111/j.1365-2141.2004.05163.x
- [118] Pan B, Yu B, Ren H. High-density lipoprotein nitration and chlorination catalyzed by myeloperoxidase impair its effect of promoting endothelial repair. *Free Radical Biology & Medicine*. 2013;**60**:272-281. DOI: 10.1016/j.freeradbiomed.2013.1002.1004
- [119] Matsunaga T, Nakajima T, Sonoda M. Modulation of reactive oxygen species in endothelial cells by peroxy-nitrite-treated lipoproteins. *Journal of Biochemistry*. 2001;**130**:285-293. DOI: 10.1093/oxfordjournals.jbchem.a002984
- [120] Wang Y, Ji L, Jiang R. Oxidized high-density lipoprotein induces the proliferation and migration of vascular smooth muscle cells by promoting the production of ROS. *Journal of Atherosclerosis and Thrombosis*. 2014;**21**:204-216. DOI: 10.1177/1074149513509448
- [121] Pan B, Ren H, Lv X. Hypochlorite-induced oxidative stress elevates the capability of HDL in promoting breast cancer metastasis. *Journal of Translational Medicine*. 2012;**10**:65. DOI: 10.1186/1479-5876-10-65
- [122] Kontush A, Chapman MJ. Why is HDL functionally deficient in type 2 diabetes? *Current Diabetes Reports*. 2008;**8**:51-59. DOI: 10.1007/s11892-008-0010-5
- [123] Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. *Nature Clinical Practice. Endocrinology & Metabolism*. 2009;**5**:150-159. DOI: 10.1038/ncpendmet1066
- [124] Matsuki K, Tamasawa N, Yamashita M. Metformin restores impaired HDL-mediated cholesterol efflux due to glycation. *Atherosclerosis*. 2009;**206**:434-438. DOI: 10.1016/j.atherosclerosis.2009.03.003
- [125] Hoang A, Murphy AJ, Coughlan MT. Advanced glycation of apolipoprotein A-I impairs its anti-atherogenic properties. *Diabetologia*. 2007;**50**:1770-1779. DOI: 10.1007/s00125-007-0718-9
- [126] Nobecourt E, Jacqueminet S, Hansel B. Defective antioxidative activity of small dense HDL3 particles in type 2 diabetes: Relationship to elevated oxidative stress and hyperglycaemia. *Diabetologia*. 2005;**48**:529-538. DOI: 10.1007/s00125-004-1655-5
- [127] Murakami H, Tanabe J, Tamasawa N. Reduction of paraoxonase-1 activity may contribute the qualitative impairment of HDL particles in patients with type 2 diabetes. *Diabetes Research and Clinical Practice*. 2013;**99**:30-38. DOI: 10.1016/j.diabetes.2012.10.022
- [128] Tsun JG, Shiu SW, Wong Y. Impact of serum amyloid A on cellular cholesterol efflux to serum in type 2 diabetes mellitus. *Atherosclerosis*. 2013;**231**:405-410. DOI: 10.1016/j.atherosclerosis.2013.10.008

- [129] Wang J, Liu K, Shen L. Small interfering RNA to c-myc inhibits vein graft restenosis in a rat vein graft model. *The Journal of Surgical Research*. 2011;**169**:e85-e91. DOI: 10.1016/j.jss.2011.03.060
- [130] Sorrentino SA, Besler C, Rohrer L. Endothelial-vasoprotective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release niacin therapy. *Circulation*. 2010;**121**:110-122. DOI: 10.1161/CIRCULATIONAHA.108.836346
- [131] Pan B, Ma Y, Ren H. Diabetic HDL is dysfunctional in stimulating endothelial cell migration and proliferation due to down regulation of SR-BI expression. *PLoS One*. 2012;**7**:e48530. DOI: 10.1371/journal.pone.0048530
- [132] Pan B, Ren H, He Y. HDL of patients with type 2 diabetes mellitus elevates the capability of promoting breast cancer metastasis. *Clinical Cancer Research*. 2012;**18**:1246-1256. DOI: 10.1158/1078-0432.CCR-11-0817
- [133] Tong X, Peng H, Liu D. High-density lipoprotein of patients with type 2 diabetes mellitus upregulates cyclooxygenase-2 expression and prostacyclin I-2 release in endothelial cells: Relationship with HDL-associated sphingosine-1-phosphate. *Cardiovascular Diabetology*. 2013;**12**:27. DOI: 10.1186/1475-2840-12-27
- [134] Srivastava RAK. Dysfunctional HDL in diabetes mellitus and its role in the pathogenesis of cardiovascular disease. *Molecular and Cellular Biochemistry*. 2018;**440**:167-187. DOI: 10.1007/s11010-017-3165-z
- [135] Nobecourt E, Davies MJ, Brown BE. The impact of glycation on apolipoprotein A-I structure and its ability to activate lecithin:cholesterol acyltransferase. *Diabetologia*. 2007;**50**:643-653. DOI: 10.1007/s00125-006-0574-z
- [136] Nobecourt E, Tabet F, Lambert G. Nonenzymatic glycation impairs the antiinflammatory properties of apolipoprotein A-I. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2010;**30**:766-772. DOI: 10.1161/ATVBAHA.109.201715
- [137] Liu D, Ji L, Zhao M. Lysine glycation of apolipoprotein A-I impairs its anti-inflammatory function in type 2 diabetes mellitus. *Journal of Molecular and Cellular Cardiology*. 2018;**122**:47-57. DOI: 10.1016/j.yjmcc.2018.08.001
- [138] Ueda M, Hayase Y, Mashiba S. Establishment and evaluation of 2 monoclonal antibodies against oxidized apolipoprotein A-I (apoA-I) and its application to determine blood oxidized apoA-I levels. *Clinical Chimica Acta*. 2007;**378**:105-111. DOI: 10.1016/j.cca.2006.11.002
- [139] Kotani K, Sakane N, Ueda M. Oxidized high-density lipoprotein is associated with increased plasma glucose in non-diabetic dyslipidemic subjects. *Clinical Chimica Acta*. 2012;**414**:125-129. DOI: 10.1016/j.cca.2012.08.021
- [140] Perez-Mendez O, Pacheco HG, Martinez-Sanchez C. HDL-cholesterol in coronary artery disease risk: Function or structure? *Clinical Chimica Acta*. 2014;**429**:111-122. DOI: 10.1016/j.cca.2013.12.001
- [141] Kontush A. HDL particle number and size as predictors of cardiovascular disease. *Frontiers in Pharmacology*. 2015;**6**:218. DOI: 10.3389/fphar.2015.00218
- [142] Superko HR, Pendyala L, Williams PT. High-density lipoprotein subclasses and their relationship to cardiovascular disease. *The Journal of Clinical Lipidology*. 2012;**6**:496-523. DOI: 10.1016/j.jacl.2012.03.001

- [143] Parish S, Offer A, Clarke R. Lipids and lipoproteins and risk of different vascular events in the MRC/BHF heart protection study. *Circulation*. 2012;**125**:2469-2478. DOI: 10.1161/CIRCULATIONAHA.111.073684
- [144] Mora S, Glynn RJ, Ridker PM. High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. *Circulation*. 2013;**128**:1189-1197. DOI: 10.1161/CIRCULATIONAHA.113.002671
- [145] Mackey RH, Greenland P, Goff DC. High-density lipoprotein cholesterol and particle concentrations, carotid atherosclerosis, and coronary events: MESA (multi-ethnic study of atherosclerosis). *The Journal of American College of Cardiology*. 2012;**60**:508-516. DOI: 10.1016/j.jacc.2012.03.060
- [146] May HT, Anderson JL, Winegar DA. Utility of high density lipoprotein particle concentration in predicting future major adverse cardiovascular events among patients undergoing angiography. *Clinical Biochemistry*. 2016;**49**:1122-1126. DOI: 10.1016/j.clinbiochem.2016.09.004
- [147] Mutharasan RK, Foit L, Thaxton CS. High-density lipoproteins for therapeutic delivery systems. *Journal of Materials Chemistry B*. 2016;**4**:188-197. DOI: 10.1039/C5TB01332A
- [148] Kuai R, Li D, Chen YE. High-density lipoproteins: Nature's multifunctional nanoparticles. *ACS Nano*. 2016;**10**:3015-3041. DOI: 10.1021/acsnano.5b07522
- [149] Varshosaz J, Vakilzadeh H, Ghassami E. Use of lipoprotein like nanoparticles used in drug and gene delivery. *Current Pharmaceutical Design*. 2016;**22**:3466-3485. DOI: CPD-EPUB-73561
- [150] Duivenvoorden R, Tang J, Cormode DP. A statin-loaded reconstituted high-density lipoprotein nanoparticle inhibits atherosclerotic plaque inflammation. *Nature Communications*. 2014;**5**:3065. DOI: 10.1038/ncomms4065
- [151] Jung C, Kaul MG, Bruns OT. Intraperitoneal injection improves the uptake of nanoparticle-labeled high-density lipoprotein to atherosclerotic plaques compared with intravenous injection: A multimodal imaging study in ApoE knockout mice. *Circulation. Cardiovascular Imaging*. 2014;**7**:303-311. DOI: 10.1161/CIRCIMAGING.113.000607
- [152] McMahon KM, Foit L, Angeloni NL. Synthetic high-density lipoprotein-like nanoparticles as cancer therapy. *Cancer Treatment and Research*. 2015;**166**:129-150. DOI: 10.1007/978-3-319-16555-4_6
- [153] Raut S, Mooberry L, Sabnis N. Reconstituted HDL: Drug delivery platform for overcoming biological barriers to cancer therapy. *Frontiers in Pharmacology*. 2018;**9**:1154. DOI: 10.3389/fphar.2018.01154
- [154] Subramanian C, Kuai R, Zhu Q. Synthetic high-density lipoprotein nanoparticles: A novel therapeutic strategy for adrenocortical carcinomas. *Surgery*. 2016;**159**:284-295. DOI: 10.1016/j.surg.2015.08.023
- [155] Shah S, Chib R, Raut S. Photophysical characterization of anticancer drug valrubicin in rHDL nanoparticles and its use as an imaging agent. *Journal of Photochemistry and Photobiology. B Biology*. 2016;**155**:60-65. DOI: 10.1016/j.jphotobiol.2015.12.007
- [156] Yang S, Damiano MG, Zhang H. Biomimetic, synthetic HDL nanostructures for lymphoma. *Proceedings of the National Academy of Sciences of the United States of America*. 2013;**110**:2511-2516. DOI: 10.1073/pnas.1213657110

- [157] Tripathy S, Vinokour E, McMahon KM. High density lipoprotein nanoparticles deliver RNAi to endothelial cells to inhibit angiogenesis. *Particle & Particle Systems Characterization*. 2014;**31**:1141-1150. DOI: 10.1002/ppsc.201400036
- [158] Remaley AT, Thomas F, Stonik JA. Synthetic amphipathic helical peptides promote lipid efflux from cells by an ABCA1-dependent and an ABCA1-independent pathway. *Journal of Lipid Research*. 2003;**44**:828-836. DOI: 10.1194/jlr.M200475-JLR200
- [159] Anantharamaiah GM, Jones JL, Brouillette CG. Studies of synthetic peptide analogs of the amphipathic helix. Structure of complexes with dimyristoyl phosphatidylcholine. *The Journal of Biological Chemistry*. 1985;**260**:10248-10255
- [160] Datta G, Chaddha M, Hama S. Effects of increasing hydrophobicity on the physical-chemical and biological properties of a class A amphipathic helical peptide. *Journal of Lipid Research*. 2001;**42**:1096-1104
- [161] Navab M, Anantharamaiah GM, Reddy ST. Apolipoprotein A-I mimetic peptides. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2005;**25**:1325-1331. DOI: 10.1161/01.ATV.0000165694.39518.95
- [162] Navab M, Anantharamaiah GM, Hama S. Oral administration of an Apo A-I mimetic peptide synthesized from D-amino acids dramatically reduces atherosclerosis in mice independent of plasma cholesterol. *Circulation*. 2002;**105**:290-292. DOI: 10.1161/hc0302.103711
- [163] Navab M, Ruchala P, Waring AJ. A novel method for oral delivery of apolipoprotein mimetic peptides synthesized from all L-amino acids. *Journal of Lipid Research*. 2009;**50**:1538-1547. DOI: 10.1194/jlr.M800539-JLR200
- [164] Tang C, Vaughan AM, Anantharamaiah GM. Janus kinase 2 modulates the lipid-removing but not protein-stabilizing interactions of amphipathic helices with ABCA1. *Journal of Lipid Research*. 2006;**47**:107-114. DOI: 10.1194/jlr.M500240-JLR200
- [165] Liu D, Ding Z, Wu M. The apolipoprotein A-I mimetic peptide, D-4F, alleviates ox-LDL-induced oxidative stress and promotes endothelial repair through the eNOS/HO-1 pathway. *Journal of Molecular and Cellular Cardiology*. 2017;**105**:77-88. DOI: 10.1016/j.yjmcc.2017.01.017
- [166] Ou Z-J, Li L, Liao X-L. Apolipoprotein AI mimetic peptide inhibits atherosclerosis by altering plasma metabolites in hypercholesterolemia. *American Journal of Physiology, Endocrinology and Metabolism*. 2012;**303**:E683-E694. DOI: 10.1152/ajpendo.00136.2012
- [167] Baotic I, Ge Z-D, Sedlic F. Apolipoprotein A-1 mimetic D-4F enhances isoflurane-induced eNOS signaling and cardioprotection during acute hyperglycemia. *American Journal of Physiology, Heart and Circulatory Physiology*. 2013;**305**:H219-H227. DOI: 10.1152/ajpheart.00850.2012
- [168] Xu W, Qian M, Huang C. Comparison of mechanisms of endothelial cell protections between high-density lipoprotein and apolipoprotein A-I mimetic peptide. *Frontiers in Pharmacology*. 2019;**10**:817. DOI: 10.3389/fphar.2019.00817
- [169] Chattopadhyay A, Navab M, Hough G. A novel approach to oral apoA-I mimetic therapy. *Journal of Lipid Research*. 2013;**54**:995-1010. DOI: 10.1194/jlr.M033555
- [170] Anantharamaiah GM, Mishra VK, Garber DW. Structural requirements for antioxidative and anti-inflammatory properties of apolipoprotein A-I

mimetic peptides. *Journal of Lipid Research*. 2007;**48**:1915-1923. DOI: 10.1194/jlr.R700010-JLR200

[171] Van Lenten BJ, Wagner AC, Jung CL. Anti-inflammatory apoA-I-mimetic peptides bind oxidized lipids with much higher affinity than human apoA-I. *Journal of Lipid Research*. 2008;**49**:2302-2311. DOI: 10.1194/jlr.M800075-JLR200

[172] D'Souza W, Stonik JA, Murphy A. Structure/function relationships of apolipoprotein A-I mimetic peptides: Implications for antiatherogenic activities of high-density lipoprotein. *Circulation Research*. 2010;**107**:217-227. DOI: 10.1161/CIRCRESAHA.110.216507

[173] Amar MJ, D'Souza W, Turner S. 5A apolipoprotein mimetic peptide promotes cholesterol efflux and reduces atherosclerosis in mice. *The Journal of Pharmacology and Experimental Therapeutics*. 2010;**334**:634-641. DOI: 10.1124/jpet.110.167890

[174] Yao X, Dai C, Fredriksson K. 5A, an apolipoprotein A-I mimetic peptide, attenuates the induction of house dust mite-induced asthma. *Journal of Immunology (Baltimore, Md.:1950)*. 2011;**186**:576-583. DOI: 10.4049/jimmunol.1001534

[175] Getz GS, Reardon CA. Apoprotein E as a lipid transport and signaling protein in the blood, liver, and artery wall. *Journal of Lipid Research*. 2009;**50**(Suppl):S156-S161. DOI: 10.1194/jlr.R800058-JLR200

[176] Bielicki JK, Zhang H, Cortez Y. A new HDL mimetic peptide that stimulates cellular cholesterol efflux with high efficiency greatly reduces atherosclerosis in mice. *Journal of Lipid Research*. 2010;**51**:1496-1503. DOI: 10.1194/jlr.M003665

[177] Garber DW, Handattu S, Aslan I. Effect of an arginine-rich amphipathic

helical peptide on plasma cholesterol in dyslipidemic mice. *Atherosclerosis*. 2003;**168**:229-237. DOI: 10.1016/S0021-9150(03)00101-1

[178] Nayyar G, Handattu SP, Monroe CE. Two adjacent domains (141-150 and 151-160) of apoE covalently linked to a class A amphipathic helical peptide exhibit opposite atherogenic effects. *Atherosclerosis*. 2010;**213**:449-457. DOI: 10.1016/j.atherosclerosis.2010.09.030

[179] Nayyar G, Garber DW, Palgunachari MN. Apolipoprotein E mimetic is more effective than apolipoprotein A-I mimetic in reducing lesion formation in older female apo E null mice. *Atherosclerosis*. 2012;**224**:326-331. DOI: 10.1016/j.atherosclerosis.2012.05.040

[180] Baryliski M, Toth PP, Nikolic D. Emerging therapies for raising high-density lipoprotein cholesterol (HDL-C) and augmenting HDL particle functionality. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2014;**28**:453-461. DOI: 10.1016/j.beem.2013.11.001

[181] Bailey D, Jahagirdar R, Gordon A. RVX-208: A small molecule that increases apolipoprotein A-I and high-density lipoprotein cholesterol in vitro and in vivo. *Journal of the American College of Cardiology*. 2010;**55**:2580-2589. DOI: 10.1016/j.jacc.2010.02.035

[182] Nicholls SJ, Gordon A, Johansson J. Efficacy and safety of a novel oral inducer of apolipoprotein a-I synthesis in statin-treated patients with stable coronary artery disease a randomized controlled trial. *Journal of the American College of Cardiology*. 2011;**57**:1111-1119. DOI: 10.1016/j.jacc.2010.11.015

[183] Picaud S, Wells C, Felletar I. RVX-208, an inhibitor of BET transcriptional regulators with selectivity for the second bromodomain. *Proceedings*

of the National Academy of Sciences of the United States of America. 2013;**110**:19754-19759. DOI: 10.1073/pnas.1310658110

[184] McLure KG, Gesner EM, Tsujikawa L. RVX-208, an inducer of ApoA-I in humans, is a BET bromodomain antagonist. *PLoS One*. 2013;**8**:e83190. DOI: 10.1371/journal.pone.0083190

[185] Jahagirdar R, Zhang H, Azhar S. A novel BET bromodomain inhibitor, RVX-208, shows reduction of atherosclerosis in hyperlipidemic ApoE deficient mice. *Atherosclerosis*. 2014;**236**:91-100. DOI: 10.1016/j.atherosclerosis.2014.06.008

[186] Gilham D, Wasiak S, Tsujikawa LM. RVX-208, a BET-inhibitor for treating atherosclerotic cardiovascular disease, raises ApoA-I/HDL and represses pathways that contribute to cardiovascular disease. *Atherosclerosis*. 2016;**247**:48-57. DOI: 10.1016/j.atherosclerosis.2016.01.036

[187] Tsujikawa LM, Fu L, Das S. Apabetalone (RVX-208) reduces vascular inflammation in vitro and in CVD patients by a BET-dependent epigenetic mechanism. *Clinical Epigenetics*. 2019;**11**:102. DOI: 10.1186/s13148-019-0696-z

[188] Siebel AL, Trinh SK, Formosa MF. Effects of the BET-inhibitor, RVX-208 on the HDL lipidome and glucose metabolism in individuals with prediabetes: A randomized controlled trial. *Metabolism*. 2016;**65**:904-914. DOI: 10.1016/j.metabol.2016.03.002

[189] Wasiak S, Gilham D, Tsujikawa LM. Downregulation of the complement cascade in vitro, in mice and in patients with cardiovascular disease by the BET protein inhibitor apabetalone (RVX-208). *Journal of Cardiovascular Translational Research*. 2017;**10**:337-347. DOI: 10.1007/s12265-017-9755-z

[190] Gilham D, Tsujikawa LM, Sarsons CD. Apabetalone downregulates factors and pathways associated with vascular calcification. *Atherosclerosis*. 2019;**280**:75-84. DOI: 10.1016/j.atherosclerosis.2018.11.002

[191] Haarhaus M, Ray KK, Nicholls SJ. Apabetalone lowers serum alkaline phosphatase and improves cardiovascular risk in patients with cardiovascular disease. *Atherosclerosis*. 2019;**290**:59-65. DOI: 10.1016/j.atherosclerosis.2019.09.002

[192] Shishikura D, Kataoka Y, Honda S. The effect of bromodomain and extra-terminal inhibitor apabetalone on attenuated coronary atherosclerotic plaque: Insights from the ASSURE trial. *American Journal of Cardiovascular Drugs: Drugs, Devices, and Other Interventions*. 2019;**19**:49-57. DOI: 10.1007/s40256-018-0298-8

[193] Ghosh GC, Bhadra R, Ghosh RK. RVX 208: A novel BET protein inhibitor, role as an inducer of apo A-I/ HDL and beyond. *Cardiovascular Therapeutics*. 2017;**35**:e12265. DOI: 10.1111/1755-5922.12265

[194] Nicholls SJ, Ray KK, Johansson JO. Selective BET protein inhibition with apabetalone and cardiovascular events: A pooled analysis of trials in patients with coronary artery disease. *American Journal of Cardiovascular Drugs: Drugs, Devices, and Other Interventions*. 2018;**18**:109-115. DOI: 10.1007/s40256-017-0250-3

[195] Naik SU, Wang X, Da Silva JS. Pharmacological activation of liver X receptors promotes reverse cholesterol transport in vivo. *Circulation*. 2006;**113**:90-97. DOI: 10.1161/CIRCULATIONAHA.105.560177

[196] Terasaka N, Hiroshima A, Koieyama T. T-0901317, a synthetic liver X receptor ligand, inhibits development of atherosclerosis in

LDL receptor-deficient mice. *FEBS Letters*. 2003;**536**:6-11. DOI: 10.1016/S0014-5793(02)03578-0

[197] Levin N, Bischoff ED, Daige CL. Macrophage liver X receptor is required for antiatherogenic activity of LXR agonists. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2005;**25**:135-142. DOI: 10.1161/01.ATV.0000150044.84012.68

[198] Oosterveer MH, Grefhorst A, Groen AK. The liver X receptor: Control of cellular lipid homeostasis and beyond implications for drug design. *Progress in Lipid Research*. 2010;**49**:343-352. DOI: 10.1016/j.plipres.2010.03.002

[199] Rigamonti E, Helin L, Lestavel S. Liver X receptor activation controls intracellular cholesterol trafficking and esterification in human macrophages. *Circulation Research*. 2005;**97**:682-689. DOI: 10.1161/01.RES.0000184678.43488.9f

[200] Peng D, Hiipakka RA, Xie JT. A novel potent synthetic steroidal liver X receptor agonist lowers plasma cholesterol and triglycerides and reduces atherosclerosis in LDLR(-/-) mice. *British Journal of Pharmacology*. 2011;**162**:1792-1804. DOI: 10.1111/j.1476-5381.2011.01202.x

[201] Quinet EM, Basso MD, Halpern AR. LXR ligand lowers LDL cholesterol in primates, is lipid neutral in hamster, and reduces atherosclerosis in mouse. *Journal of Lipid Research*. 2009;**50**:2358-2370. DOI: 10.1194/jlr.M900037-JLR200

[202] Katz A, Udata C, Ott E. Safety, pharmacokinetics, and pharmacodynamics of single doses of LXR-623, a novel liver X-receptor agonist, in healthy participants. *Journal of Clinical Pharmacology*. 2009;**49**:643-649. DOI: 10.1177/0091270009335768

[203] Bradley MN, Hong C, Chen M. Ligand activation of LXR beta reverses atherosclerosis and cellular cholesterol overload in mice lacking LXR alpha and apoE. *The Journal of Clinical Investigation*. 2007;**117**:2337-2346. DOI: 10.1172/JCI31909

[204] Lo Sasso G, Murzilli S, Salvatore L. Intestinal specific LXR activation stimulates reverse cholesterol transport and protects from atherosclerosis. *Cell Metabolism*. 2010;**12**:187-193. DOI: 10.1016/j.cmet.2010.07.002

[205] Yasuda T, Grillot D, Billheimer JT. Tissue-specific liver X receptor activation promotes macrophage reverse cholesterol transport in vivo. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2010;**30**:781-786. DOI: 10.1161/ATVBAHA.109.195693

[206] Mencarelli A, Fiorucci S. FXR an emerging therapeutic target for the treatment of atherosclerosis. *Journal of Cellular and Molecular Medicine*. 2010;**14**:79-92. DOI: 10.1111/j.1582-4934.2009.00997.x

[207] Hambruch E, Miyazaki-Anzai S, Hahn U. Synthetic farnesoid X receptor agonists induce high-density lipoprotein-mediated transhepatic cholesterol efflux in mice and monkeys and prevent atherosclerosis in cholesteryl ester transfer protein transgenic low-density lipoprotein receptor (-/-) mice. *The Journal of Pharmacology and Experimental Therapeutics*. 2012;**343**:556-567. DOI: 10.1124/jpet.112.196519

[208] Fiorucci S, Cipriani S, Baldelli F. Bile acid-activated receptors in the treatment of dyslipidemia and related disorders. *Progress in Lipid Research*. 2010;**49**:171-185. DOI: 10.1016/j.plipres.2009.11.001

[209] Canfran-Duque A, Ramirez CM, Goedeke L. microRNAs and HDL life cycle. *Cardiovascular Research*.

2014;**103**:414-422. DOI: 10.1093/cvr/cvu140

[210] Baldan A, de Aguiar Vallim TQ. miRNAs and high-density lipoprotein metabolism. *Biochimica et Biophysica Acta*. 2016;**1861**:2053-2061. DOI: 10.1016/j.bbali.2016.01.021

[211] Canfran-Duque A, Lin CS, Goedeke L. Micro-RNAs and high-density lipoprotein metabolism. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2016;**36**:1076-1084. DOI: 10.1161/ATVBAHA.116.307028

[212] Rayner KJ, Moore KJ. MicroRNA control of high-density lipoprotein metabolism and function. *Circulation Research*. 2014;**114**:183-192. DOI: 10.1161/CIRCRESAHA.114.300645

[213] Rayner KJ, Suarez Y, Davalos A. MiR-33 contributes to the regulation of cholesterol homeostasis. *Science*. 2010;**328**:1570-1573. DOI: 10.1126/science.1189862

[214] Horie T, Baba O, Kuwabara Y. MicroRNA-33 deficiency reduces the progression of atherosclerotic plaque in ApoE^{-/-} mice. *Journal of American Heart Association*. 2012;**1**:e003376. DOI: 10.1161/JAHA.112.003376

[215] Fernandez-Hernando C, Moore KJ. MicroRNA modulation of cholesterol homeostasis. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2011;**31**:2378-2382. DOI: 10.1161/ATVBAHA.111.226688

[216] Rayner KJ, Esau CC, Hussain FN. Inhibition of miR-33a/b in non-human primates raises plasma HDL and lowers VLDL triglycerides. *Nature*. 2011;**478**:404-407. DOI: 10.1038/nature10486

[217] Karunakaran D, Thrush AB, Nguyen MA. Macrophage mitochondrial energy status regulates cholesterol efflux and is enhanced by anti-miR33 in

atherosclerosis. *Circulation Research*. 2015;**117**:266-278. DOI: 10.1161/CIRCRESAHA.117.305624

[218] Rotllan N, Ramirez CM, Aryal B. Therapeutic silencing of microRNA-33 inhibits the progression of atherosclerosis in Ldlr^{-/-} mice—Brief report. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2013;**33**:1973-1977. DOI: 10.1161/ATVBAHA.113.301732

[219] Distel E, Barrett TJ, Chung K. miR33 inhibition overcomes deleterious effects of diabetes mellitus on atherosclerosis plaque regression in mice. *Circulation Research*. 2014;**115**:759-769. DOI: 10.1161/CIRCRESAHA.115.304164

[220] de Aguiar Vallim TQ, Tarling EJ, Kim T. MicroRNA-144 regulates hepatic ATP binding cassette transporter A1 and plasma high-density lipoprotein after activation of the nuclear receptor farnesoid X receptor. *Circulation Research*. 2013;**112**:1602-1612. DOI: 10.1161/CIRCRESAHA.112.300648

[221] Ramirez CM, Rotllan N, Vlassov AV. Control of cholesterol metabolism and plasma high-density lipoprotein levels by microRNA-144. *Circulation Research*. 2013;**112**:1592-1601. DOI: 10.1161/CIRCRESAHA.112.300626

[222] Kang MH, Zhang LH, Wijesekara N. Regulation of ABCA1 protein expression and function in hepatic and pancreatic islet cells by miR-145. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2013;**33**:2724-2732. DOI: 10.1161/ATVBAHA.113.302004

[223] Goedeke L, Rotllan N, Canfran-Duque A. MicroRNA-148a regulates LDL receptor and ABCA1 expression to control circulating lipoprotein levels. *Nature Medicine*. 2015;**21**:1280-1289. DOI: 10.1038/nm.3949

[224] Wang L, Jia XJ, Jiang HJ.
MicroRNAs 185, 96, and 223 repress
selective high-density lipoprotein
cholesterol uptake through
posttranscriptional inhibition.
Molecular and Cellular Biology.
2013;**33**:1956-1964. DOI: 10.1128/
MCB.01580-12

[225] Aryal B, Singh AK, Rotllan N.
MicroRNAs and lipid metabolism.
Current Opinion in Lipidology.
2017;**28**:273-280. DOI: 10.1097/
MOL.0000000000000420

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