Chapter 4

Role of HDL-Associated Proteins and Lipids in the Regulation of Inflammation

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Abstract

Lipoproteins are complexes of lipids and proteins that carry water-insoluble cholesterol in the bloodstream. While cholesterol is required for normal cell function, hypercholesterolemia contributes to the development of cardiovascular disease (CVD). Increased low-density lipoprotein (LDL) is a major risk factor for CVD. Reduced high-density lipoprotein (HDL) levels are inversely related to CVD risk, suggesting a protective role for HDL. Several diseases, including atherosclerosis, diabetes, chronic kidney disease and rheumatoid arthritis, have been identified where HDL levels are decreased or function is compromised. HDLs are spherical particles with a hydrophobic core of cholesteryl esters surrounded by a monolayer of phospholipids, proteins and unesterified cholesterol. Apolipoprotein (apo) A-I, the major protein component of HDL, plays an important role in the assembly and function of HDL. One of the major functions of HDL is to mediate cellular cholesterol efflux and the transfer of cholesterol from extrahepatic tissues to the liver for excretion into the bile. In addition to regulating cholesterol metabolism, HDL also exhibits antioxidative, antithrombotic and anti-inflammatory properties. Under certain conditions, however, HDL may undergo biochemical modification resulting in the formation of a particle with pro-inflammatory properties. This review will focus on the variable properties of HDL under normal physiological conditions and in the context of inflammation.

Keywords: HDL, inflammation, lipid composition, protein composition, function, macrophage mitochondria

1. Introduction

Hypercholesterolemia is an important determinant of cardiovascular disease (CVD), the leading cause of death globally [1]. Cholesterol, among other lipids, is carried in the bloodstream

from the liver to different parts of the body by lipoproteins, complex particles composed of lipids and proteins. There are four major lipoproteins that can be classified on the basis of their density: chylomicrons, very low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) [2]. Chylomicrons, VLDL and LDL are larger particles with densities ranging from 0.95 to 1.063 g/ml. HDL is a mixture of spherical particles ranging in size from 7 to 12 nm in diameter and 1.063–1.21 g/ml in density. Epidemiological studies have established an inverse relationship between HDL cholesterol and CVD risk [3, 4]. Thus, a reduction in plasma HDL levels represents an important risk factor for CVD. Results of clinical trials demonstrate that lowering LDL levels reduces CVD risk [5, 6]. Evidence supporting a role for elevated HDL in reducing CVD risk, however, is still forthcoming. Clinical trials have shown that torcetrapib, dalcetrapib and extended-release niacin significantly increase circulating HDL levels; however, this was not associated with improved outcomes [7–9]. On the other hand, raising plasma HDL by infusion or overexpression of apoA-I in murine models was shown to reduce atherogenic lesion progression [10]. One hypothesis to explain this disparity proposes that the "quality" or functional status of HDL may be a better indicator of CVD risk than plasma levels of HDL per se [11]. This review will focus on the structure-function relationship of HDL and how it influences responses to the lipoprotein in the context of inflammation.

HDL particles have a neutral core of cholesteryl ester and triglycerides (TG) surrounded by a monolayer of phospholipids, free cholesterol (FC) and protein. ApoA-I is the major protein associated with HDL particles and is synthesized in the liver and small intestine. Phospholipids and cholesterol are transferred to apoA-I by a process mediated by the ATP-binding cassette transporter type 1 (ABCA1) [12, 13] resulting in the formation of a lipid poor, dense particle called preβ-HDL. This particle plays an important role in reverse cholesterol transport, a process by which cholesterol is removed from cells. Although these particles have been predominantly studied under in vitro conditions, little information is available regarding the presence or functional significance of preβ-HDL in vivo [14]. HDL isolated from plasma by sequential ultracentrifugation yields two major subpopulations: HDL2, a large, light, lipid-rich particle (d1.063–1.125 g/ml), and HDL3, a smaller, denser protein-rich particle (d1.125–1.21 g/ml). These two particles can be further subdivided into five distinct populations: HDL2b, HDL2a, HDL3a, HDL3b and HDL3c [15]. These heterogeneous particles vary in their lipid and protein composition, forming particles of varying density, charge, and antigenicity. They also possess discrete functional properties.

2. HDL structural components

***The HDL lipidome*:** Phospholipids (PL) represent the major lipid component of HDL, constituting about 50% by weight of all the lipids [15]. Phosphatidylcholine (PC), with a carbon backbone of varying length and saturation, is the major PL species. Lysophosphatidylcholine (LPC), phosphatidylethanolamine (PE), phosphatidylinositol (PI) and plasmalogens are also present at lower, but significant, amounts (greater than 1% of total HDL lipids by weight). Other phospholipids (phosphatidylglycerol (PG), phosphatidylserine (PS), phosphatidic acid (PA) and cardiolipin) constitute less than 1% of total HDL lipids by weight.

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Sphingolipids are also well-represented in HDL particles. Sphingomyelin (SM) accounts for 5–10% by weight of total HDL lipids [15]. SM is converted to ceramide by sphingomyelinase [16]. Ceramide constitutes 0.05% by weight of total HDL lipids. Ceraminidase converts ceramide to sphingosine. Finally, the enzyme sphingosine kinase converts sphingosine to sphingosine 1-phosphate (S1P) [16]. S1P, as well as ceramide-1-phosphate, are carried by HDL and are potent signaling molecules that regulate cell growth, survival and differentiation [17]. S1P plays an important role in the suppression of inflammation [17]. S1P binding to HDL requires its physical interaction with apo M [17, 18]. Sphingosylphosphorylcholine and lysosulfatide are additional, biologically active lysosphingolipids carried by HDL [15]. The principal lipids associated with HDL particles are summarized in **Table 1**.

Proteins	**Lipids**
Apolipoproteins (AI-II, A-V, C-I-IV, D, E, F, M, H, O)	Phospholipids:
CETP	PC, PE, PI, PG, PS, PA
PAF-AH	
PLTP	Sphingolipids:
LCAT	SM
PON1, PON3	Ceramides
SAA1, SAA2, SAA4	S1P
Albumin	Sphingosylphosphorylcholine
Transthyretin	Lysosulfatide
Hemoglobin	
Hemopexin	
Transferrin	
Ceruloplasmin	
Vitamin D binding protein	
Complement	

Table 1. Normal protein and lipid components of HDL.

The HDL proteome: The HDL proteome has been characterized by several groups over the past 10 years. Using mass spectroscopy, the presence of at least 85 proteins on HDL have been reported [19]. These fall into different regulatory categories: lipid metabolism, acute phase response (APR), hemostasis, immune response, metal binding, vitamin transport, proteinase inhibitor and complement regulation [19, 20]. A representative list of HDL-associated proteins is shown in **Table 1**. Among these, the lipid metabolism group is the largest and contains apoA-I as well as other apolipoproteins (**Table 1**). As mentioned above, HDL exists as multiple sub-species. The proteins, lecithin-cholesterol acyltransferase (LCAT), phospholipid transfer protein (PLTP) and cholesteryl ester transfer protein (CETP), play a major role in converting HDL from one sub-species to another. APR proteins such as apo A-IV, SAA1 and SAA2 regulate lipid metabolism and are also present along with Apo J, a protein involved in

lipid metabolism and complement regulation. Surprisingly, a variety of other proteins with diverse functions such as hemoglobin, hemopexin and transferrin (iron metabolism), ceruloplasmin (metal binding), and vitamin D binding protein (vitamin binding) are also seen. These are described in detail in the review by Shah et al. [19]. Thus, the protein and lipid cargo on HDL significantly influence particle function.

3. Functions of HDL

Reverse cholesterol transport: Under hypercholesterolemic conditions, the accumulation of cholesterol in macrophages leads to the formation of "foam cells" which contribute to atheroma formation. HDL is commonly referred to as the "good cholesterol". The salutary effect of HDL has been attributed to its ability to transfer cholesterol from extra-hepatic tissues to the liver for metabolism and excretion into the bile, a process called reverse cholesterol transport [21]. This is believed to be a critical antiatherogenic function of HDL. Cholesterol from macrophages is transferred to lipid-poor apoA-I [22] *via* ABCA1. The cholesterol is converted to cholesterol esters by the action of LCAT present on HDL. Sequestration of cholesterol esters in the hydrophobic core of the particle is associated with the formation of spherical HDL2 and HDL3. These mature HDL particles also incorporate cholesterol *via* an alternate transporter, the ATP-binding cassette transporter G1 (ABCG1) as well as the scavenger-receptor class B, type 1 (SR-BI) pathway [23]. Cholesterol-enriched HDL is subsequently removed from the circulation by hepatocytes and is excreted by the biliary pathway into bile and feces. In addition to mediating reverse cholesterol transport, HDL also possesses antioxidant, anti-inflammatory and antithrombotic properties. These pleiotropic effects of HDL play a major role in limiting inflammatory injury associated with leukocyte infiltration in the blood vessel wall.

***Antioxidant properties of HDL*:** Chylomicrons, VLDL and LDL are apoB-containing lipoproteins which deliver cholesterol and TG to cells and are strongly implicated in atheroma formation. The response-to-retention hypothesis postulates that [24] LDL is oxidized in the arterial wall by enzymes including myeloperoxidase (MPO), NADPH oxidase, nitric oxide synthase and lipoxygenase, resulting in the accumulation of lipid hydroperoxides (LOOH) [25]. Oxidized LDL (ox-LDL) is taken up by macrophages leading to the formation of foam cells and fatty plaques. Protein and lipid components of HDL inhibit the accumulation of LOOH in LDL and prevent the formation of ox-LDL. LOOH and phosphatidyl choline hydroperoxides (PLOOH) are transferred from LDL to HDL. This process is regulated by the lipid composition and rigidity of the HDL surface. Specifically, HDL surface rigidity is determined by the ratios of SM:PC, FC:PL and saturated to polyunsaturated fatty acids (SFA:PUFA) [26]. Zerrad-Saadi and colleagues have identified the HDL3 particle as a key mediator of LOOH transfer due its optimal surface rigidity and particle content [27].

ApoA-I is likely the major HDL protein species involved in the removal of LOOH moieties from LDL. The methionine (Met) residues 112 and 148 of apoA-I can reduce LOOHs to inactive lipid hydroxides (LOH) [28]. In addition, apoA-I removes seeding LOOH molecules from LDL [29]. In addition to apoA-I, other apolipoprotein and enzyme components of HDL, such as, apo E, apo J, apo A-II, apo L-1, apo F, apo A-IV, PON1/3, PLTP and PAF-AH, play a role in

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its antioxidant function. Proteomic analyses from the Davidson laboratory [30] demonstrate that HDL3c contains all these proteins along with apo M, apo D, apo A-II, SAA1,2 and 4 and apo C-I and apo C-II. This corroborates earlier studies showing that HDL3c has more potent antioxidant activity than other HDL subspecies [31, 32]. Thus, both lipid and protein components of HDL3c contribute to its antioxidant activity. Kontush et al. [32] have hypothesized that the protein components of HDL3c form a pocket which enables the transfer of LOOH from LDL which is further reduced by the concerted action of apolipoproteins and enzymes in this pocket [26].

***Anti-inflammatory properties of HDL*:** The role of inflammation in atherogenesis has been clearly established [33–35]. Acute and chronic inflammations are associated with monocyte adhesion/infiltration and endothelial cell activation [33–35]. HDL is known to suppress the lipopolysaccharide (LPS)-induced secretion of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ) and other pro-inflammatory mediators [36–38]. HDL also reduces inflammation by neutralizing endotoxin, further supporting its anti-inflammatory role [39]. Thus, HDL exerts its anti-inflammatory effect in multiple ways.

*Regulation of endotoxicity***:** In the context of infection, Gram-negative bacteria release LPS in the circulation which binds CD14 located in membrane rafts on cell surfaces. CD14 engagement facilitates the activation of toll-like receptor 4 (TLR4) binding, resulting in the release of pro-inflammatory cytokines such as IL-6 and TNF-α. HDL is able to inhibit this initial activation step *via* binding to lipid A, a glycolipid component of LPS, thus preventing TLR4 activation. Gram-positive bacteria release lipoteichoic acid (LTA) which, similar to LPS, binds CD14 and activates pro-inflammatory signaling *via* the TLR2/6 pathway [40, 41]. HDL additionally contributes to the inactivation of LPS and LTA by disrupting membrane rafts. In this manner, HDL mediates cholesterol and phospholipid efflux which destabilizes rafts and prevents the assembly of receptor complexes for LPS and LTA [14, 40].

Regulation of macrophage function: Macrophages are a versatile group of cells that play a critical role in regulating immunity, inflammation and lipid metabolism. Macrophage phenotype and function are regulated, in large part, by their environmental milieu [42–45]. On the basis of cell morphology and function, two populations of activated macrophages have been identified [46]. The classically activated M1 macrophage is induced by LPS and Th1 cytokines such as IFN-γ, interleukin-2 (IL-2) and TNF-α [43, 44]. These cells are pro-inflammatory and secrete inflammatory mediators (TNF-α, IL-1, IL-6, IL-15, IL-18, IL-23, IFN-γ), stimulate inducible nitric oxide synthase (iNOS) and promote the formation of reactive oxygen and nitrogen species [47]. The second macrophage phenotype, the alternatively activated M2 macrophage, is induced by IL-4, IL-10, IL-13 and glucocorticoid hormones [42–45]. M2 macrophages play an important role in the resolution of inflammation by inhibiting inflammatory cytokine expression and promoting wound healing [42–45]. HDL and apo A-I have been shown to promote the formation of anti-inflammatory M2 macrophages in human monocyte-derived macrophages [48] and mice [49]. As mentioned in the previous section, HDL3 is a key mediator of reverse cholesterol transport and possesses potent antioxidant properties. Reports from several laboratories suggest that HDL-associated S1P inhibits inflammation *via* activation of the PI3-kinase/*Akt* signaling pathway [50–52]. Pretreatment of bone marrow-derived

macrophages (BMDMs) with S1P suppressed LPS-induced secretion of TNF-α, monocyte chemoattractant protein (MCP) and IL-12 [53]. Additionally, Hughes and colleagues reported that S1P enhanced the activity of Arg1 and suppressed the NF-kB-mediated induction of iNOS [53]. These responses to S1P are associated with M2 macrophage polarization.

Regulation of mitochondrial function: The mitochondrion is a double-membraned, energy-producing organelle, which contains its own maternally inherited mitochondrial DNA [54–56]. Under normal conditions, the mitochondrial respiratory chain shuttles electrons through the respiratory complexes, consumes oxygen at Complex IV and pumps hydrogen ions from inside the mitochondria to the intermembrane space at Complexes I, III and IV. This allows ATP production to proceed at the level of Complex V (ATP synthase). Under normal conditions, oxidative phosphorylation is a tightly regulated process with heat and reactive oxygen species (ROS) being produced as byproducts.

In the presence of ox-LDL and other oxidized lipids, the mitochondrion increases the formation of ROS, which can damage the mitochondria and other organelles causing cellular dysfunction and death. HDL, by virtue of its antioxidant properties, can decrease the cellular damage caused by oxidized lipids. The HDL protein PON1 hydrolyzes cholesterol esters and phospholipids in oxidized lipoproteins [52, 57, 58] thus inhibiting mitochondrial damage in the presence of oxidized lipids [58]. Further, HDL-associated apoA-I has been implicated in electron transport chain maintenance and repair [59]. In apoA-I null mice (apoA-I$^{-/-}$), an increase in coronary ischemia-reperfusion injury is observed compared to wild-type mice [59] and is associated with a decrease in the content of the mitochondrial protein Coenzyme Q (CoQ) in cardiomyocytes. CoQ normally supports oxidative phosphorylation by shuttling electrons from Complex II to Complex III. Exogenous administration of CoQ to apo-A-I$^{-/-}$ mice attenuated myocardial infarct size compared to the injury response in untreated mice. These data indicate the importance of HDL, and specifically, apoA-I in preserving mitochondrial structure and function.

Potential mechanisms by which HDL preserves mitochondrial function include activation of the Reperfusion Injury Salvage Kinase (RISK) pathway and the Survivor Activating Factor Enhancement (SAFE) cascade. These are cell survival pathways which are known to prevent mitochondrial damage in models of ischemic pre- and postconditioning [60]. Activation of STAT3 is an important component of the SAFE pathway and results in the downregulation of pro-apoptotic factors Bax and Bad and upregulation of antiapoptotic factor Bcl-2 and the antioxidants manganese superoxide dismutase and metallothionein [60, 61]. Further, STAT3 is transported to the mitochondrion by the GRIM-19 chaperone where it inhibits the release of cytochrome c and reduces cell death [62–64]. In a rodent model of coronary artery occlusion, the administration of apoA-I was shown to decrease infarct size and inhibit mitochondrial morphological changes seen in the heart [60]. Further analyses showed that apoA-I increased the phosphorylation of *Akt* and glycogen synthase kinase 3 beta (GSK3β), known mediators of the RISK and SAFE survival pathways.

The S1P component of HDL is also able to activate the RISK And SAFE pathways [51, 52, 65]. Interestingly, studies conducted in neonatal rat cardiomyocytes showed that S1P is critically required for the phosphorylation of STAT3. In contrast, STAT3 phosphorylation was

absent in cells treated with HDL that was deficient in S1P [65]. In addition, S1P stimulates the phosphorylation of the transcription factor, forkhead box O-1 (FOXO-1), which inhibits ROS formation and apoptosis in the phosphorylated form [66, 67]. These data suggest that HDL activates RISK and SAFE pathways and inhibits ROS, mitochondrial dysfunction and cell death.

Interestingly, S1P has also been shown to regulate mitochondrial Complex IV assembly and cellular respiration by interacting with mitochondrial prohibitin-2 (PBH-2) [68]. PBH-2 acts as a scaffolding protein for mitochondria and its interaction with S1P during ischemic preconditioning of cardiomyocytes is essential for cardioprotection [68–70]. These data suggest that S1P can stabilize mitochondrial complexes and inhibit ROS formation, suggesting an alternate cardioprotective mechanism of S1P action.

Recent studies have suggested that other HDL-associated apolipoproteins play a role in preserving mitochondrial structure and function. ApoJ is expressed ubiquitously and is present on small dense HDL3 particles [71–73]. It is considered to be an antioxidant due to the presence of disulfide bonds that inhibit ROS-induced injury and preserve mitochondrial function [74]. Further, apoJ has been implicated in activating *Akt* and GSK3β and the RISK survival pathway [71]. ApoM is found in association with approximately 5% of HDL particles where it confers several cytoprotective properties that include stimulating preβ-HDL formation, facilitating reverse cholesterol transport and inhibiting LDL oxidation [75–78]. ApoM also plays an important role in the cytoprotective response to S1P by binding the sphingolipid and facilitating its incorporation into HDL particles [75, 79, 80]. It follows that overexpression of apoM in mice reduces infarct size in response to ischemia-reperfusion injury and preserves mitochondrial function by increasing the HDL content of S1P.

4. Inflammation-induced alterations in HDL structure

Changes in HDL sub-species and their function have been reported in several disease states, including atherosclerosis [4], rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) [81, 82], diabetes [83], hypertension [84] and psoriasis [85–87]. Inflammation/infection triggers an APR that causes a reduction in HDL quantity and alterations in both its lipid and protein composition. Van Lenten and colleagues [88] first reported that HDL loses its ability to inhibit LDL oxidation during the APR, demonstrating that inflammation affects the structure and function of HDL.

***Lipidome alterations*:** The phospholipid content of HDL is altered during the APR [89]. This may be due to an increase in the activity of secretory phospholipase 2 ($sPLA_2$) [90, 91]. Acute phase HDL also contains lower amounts of PE and PI along with several species of LPC with different levels of saturation. An important feature of acute phase HDL is that it contains oxidized phospholipids generated by the actions of transition metal ions, free radicals and hypochlorous acid (HOCl) [92, 93]. Formation of acute phase HDL in patients with coronary heart disease is also associated with a reduction in SM content [94]. An increase in triglycerides with a decrease in cholesteryl esters is also commonly observed in acute phase HDL [89].

Proteome alterations: Several changes in HDL-associated proteins arise in response to inflammation (**Table 2**). While a reduction in apo A-I represents perhaps the most prominent change in HDL composition, data suggest that the lipoprotein content of SAA may increase up to 1000-fold [85]. Endotoxin and inflammatory cytokines (TNF-α, IL-1β and IL-6) decrease the expression of apoA-I which leads to a decrease in circulating HDL concentration [95, 96]. In addition, an increase in the synthesis of SAA results in the displacement of apoA-I from acute phase HDL [85]. Inflammation further decreases HDL levels by inducing the upregulation of $sPLA_2$ which degrades phospholipid components of the lipoprotein particle [89]. Loss of LCAT activity [97, 98] reduces the cholesterol carrying capacity of HDL by preventing the formation of cholesterol esters. Finally, PON1 activity is reduced by inflammation in patients with RA, SLE and psoriasis and infections and is associated with a reduction in the antioxidant capacity of HDL [99–102].

Proteins[a]		**Lipids**[b]	
Increased	**Decreased**	**Increased**	**Decreased**
Serum Amyloid A (SAA)	Apo A-I	Triglycerides	Total lipid
Apo J	Apo A-II	FC	Phospholipids
$sPLA_2$	Apo C	LPC	CE
Apo E	Apo M	FFA	SM
Ceruloplasmin	LCAT		
PAF-AH	CETP		
LBP	Transferrin		
Apo A-IV	Hepatic lipase		
Apo A-V	Paraoxanase I		

[a] Adapted from Refs. [87, 96, 97, 104].
[b] Adapted from Refs. [15, 89, 94].

Table 2. Inflammation-induced changes in HDL composition.

The presence of apoM in HDL particles is thought to contribute to atheroprotection [103]. LPS and inflammatory cytokines, however, attenuate apoM mRNA levels and protein expression in Hep3B cells [104]. A decrease in serum apoM is also observed in patients with sepsis and HIV infections [104]. Further, a reduction in apoM reduces the association of S1P with HDL resulting in degradation of anti-inflammatory function [103].

The association of other apolipoproteins with HDL may impair the function of the lipoprotein. ApoO is incorporated by HDL, LDL and VLDL particles [105]. Data suggest that apoO provides structural stability for mitochondria by stabilizing the inner mitochondrial membrane and cristae [105]. Other data, however, show that overexpression of apoO degrades mitochondrial protein and increases cardiac dysfunction in hypercholesterolemic mice [106]. In cardiomyocyte cultures, upregulation of apoO was associated with an increase in ROS and apoptosis compared to control cells that were apoO-deficient [106]. ApoC is an additional, exchangeable apolipoprotein associated with HDL and apoB-containing lipoproteins. In iso-

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lated rat liver mitochondria, addition of the apoC-III isoform was shown to inhibit mitochondrial oxygen consumption and attenuate ATP formation [107]. Another study showed that enrichment of HDL with apoC-I stimulates cytochrome c release, caspase 3 cleavage and cell death in human aortic smooth muscle cells [108]. Finally, apoC-I enrichment of HDL is associated with a reduction in HDL-associated apoA-I, suggesting that loss of apoA-I and its cytoprotective effects is a component of apoC-I-mediated cell injury [107, 108]. Clearly, additional in vitro and in vivo studies are required to define the mechanistic role of specific apolipoprotein species in the development of inflammatory injury.

5. Functional consequences of acute phase HDL formation

Changes in HDL lipid and protein composition induced by the APR impair normal HDL function resulting in the formation of "dysfunctional" HDL.

Loss of cholesterol efflux ability: Since cholesterol efflux involves the participation of apoA-I, phospholipids, LCAT and CETP, several aspects of dysfunctional HDL inhibit normal reverse cholesterol transport. The reduction in apoA-I and increase in HDL-associated SAA impair cholesterol efflux capacity [109, 110]. The presence of SAA on HDL increases foam cell formation by facilitating the uptake of cholesterol esters by macrophages. At the level of the hepatocyte, this acute phase HDL impairs cholesterol uptake and degradation [111]. Decreased content of LCAT, PL and CETP on HDL also contribute to a loss of efflux activity as does the oxidative modification of apoA-I [112, 113].

Impairment of antioxidative activity: An increase in TG and decrease in cholesterol ester content in dysfunctional HDL leads to a change in conformation of the HDL particle. The formation of a TG-rich HDL particle induces structural changes in apoA-I and decreases its stability [114]. Additionally, an increase in SAA and loss of PON1 result in a reduced antioxidant capacity of the HDL particle.

Attenuation of anti-inflammatory activity: Dysfunctional HDL has an impaired capacity to counteract the action of LPS and inflammatory cytokines. The ability to regulate membrane raft cholesterol content is reduced and can thus enhance TLR activation in response to pro-inflammatory mediators [115]. Oxidation of apoA-I also results in a loss of functionality with respect to its ability to efflux cholesterol. The protein and lipid alterations observed (reduced apoA-I, cholesterol ester, PON1 and LCAT levels and increased TG and SAA levels) are also responsible for the attenuated anti-inflammatory activity observed with dysfunctional HDL.

6. Conclusions

HDL plays an important role in regulating atherogenesis *via* its ability to mediate reverse cholesterol transport. The ability of HDL to reduce inflammatory injury and oxidant stress has also been shown to reduce CVD risk. As discussed in this review, both protein and lipid components of the lipoprotein particle play critical roles in attenuating inflammation.

Identification of these cytoprotective HDL components has been facilitated by recent proteomic analyses. Under pathological conditions, HDL levels may be reduced and the lipoprotein may undergo biochemical and structural modification resulting in the formation of dysfunctional HDL with pro-inflammatory properties. It has been suggested that the anti-inflammatory status of HDL may be of greater predictive value for CVD risk than HDL levels per se [116, 117]. Therapeutic approaches that increase the functional properties of HDL may thus be superior to simply raising circulating HDL. Unfortunately, specific and reliable biomarkers for anti-inflammatory HDL have not been identified. Under ex vivo conditions, the quality of HDL can be assessed by studying lipoprotein effects of processes such as monocyte chemotaxis and endothelial inflammation. These assays, however, are cumbersome and time-consuming. Despite these drawbacks, there is significant interest in developing new pharmacotherapies that positively impact circulating lipoproteins. Randomized clinical trials have assessed effects of several classes of drugs on plasma cholesterol levels in patients at risk. Niacin and statins significantly lower LDL and were shown to induce modest increases in HDL [8]. Residual risk, however, may be present in patients with persistently low HDL despite a reduction in LDL. CETP inhibitors have been shown to increase HDL levels in animal models and in human subjects with low HDL [118, 119]. The ILLUMINATE trial tested effects of the CETP inhibitor torcetrapib on HDL and outcomes in high risk patients but was terminated early due to an increase in mortality due to off-target effects [7]. In ongoing studies, the antiatherogenic and anti-inflammatory effects of reconstituted HDL therapy as well as apolipoprotein mimetics are being evaluated. Recent exciting data also show that HDL serves as a carrier for functional miRNAs that suppress inflammation at the level of the endothelial cell [120]. miRNAs have also been identified that regulate HDL biogenesis [121]. These recent observations may lay the foundation for a new field of miRNA-based HDL therapeutics.

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