Published in final edited form as:
Curr Opin Endocrinol Diabetes Obes. 2010 April ; 17(2): 156–160. doi:10.1097/MED.0b013e328337278b.

HDL and the acute phase response

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Abstract

Purpose of review—Inflammation and the concomitant acute phase response induce marked changes in the lipoprotein profile, particularly the HDL fraction. This review describes the transfer proteins and lipases that remodel HDL and regulate its plasma levels, discusses the changes occurring in their activities during inflammation, and the influence of this altered remodeling on HDL function. The review will also discuss the contribution of the ABC transporters to the protective actions of HDL.

Recent findings—Studies using different models showed that remodeling of AP HDL *in vitro* generates pre-beta migrating particles capable of cholesterol efflux. Induction of the APR in humans resulted in a reduction of HDL phospholipids without a change in HDL-cholesterol. However, the capacity of HDL to promote cholesterol efflux *ex vivo* was impaired. Studies with ABCA1 and ABCG1 knock-out mice demonstrated anti-inflammatory roles for these transporters by virtue of reducing cell membrane free cholesterol and lipid raft content, thus attenuating pro-inflammatory signaling pathways.

Summary—It is well known that HDL has anti-inflammatory properties which are diminished during inflammation. AP HDL contains SAA which can be liberated during remodeling by CETP and $sPLA_2$, or other inflammatory factors. The ability of SAA and apoA-I to promote cholesterol efflux may confer protective effects during the APR.

Keywords

Serum amyloid A; secretory phospholipase A_2; endothelial lipase; cholesteryl ester transfer protein; ABCA1

Introduction

It is well established that, irrespective of the plasma low-density lipoprotein cholesterol (LDL-C) concentration, a low level of high density lipoprotein cholesterol (HDL-C) represents a significant independent risk factor for cardiovascular events [1]. HDL constitutes a dynamic polydisperse group of particles which are central to lipid metabolism. Its protein component is exceedingly diverse, comprising structural apolipoproteins, enzymes, co-factors for enzymes and numerous other proteins [2]. HDL should perhaps best be viewed as a phase whose constituents come and go with distinct half-lives. This understanding will lead to a better grasp of its functions such as involvement in reverse cholesterol transport (RCT) and anti-inflammatory actions [2–3]. The constant remodeling

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Disclosures: None

that HDL undergoes is particularly amplified during inflammation when serum amyloid A (SAA) and acute phase phospholipases act on the particle. This review focuses on the changes in HDL components and HDL function that occur during inflammation.

HDL remodeling

The most widely accepted function of HDL relates to RCT whereby excess cholesterol from the periphery is transported back to the liver for excretion [4]. During this process, the ATP-binding-membrane-cassette transporter A1 (ABCA1) mediates the efflux of excess cholesterol and phospholipids from peripheral cells, such as macrophages, to lipid-poor apoA-I, forming nascent HDL particles. The HDL cholesterol is further esterified in the circulation by lecithin:cholesterol acyltransferase (LCAT), and excreted by the liver after uptake either indirectly through cholesteryl ester transfer protein (CETP) mediated transfer to apoB containing lipoproteins or directly through scavenger receptor class B type I (SRBI) action. The ABCG1 transporter works in concert with ABCA1 [5] by effluxing cholesterol, mainly to spherical HDL. This mature HDL is continuously subjected to remodeling by various factors including CETP and hepatic lipase. Remodeling by these factors alters the core and shell of HDL, respectively, promoting the dissociation of lipid-poor apoA-I, which is susceptible to clearance in the kidney. On the other hand, the shedding of apoA-I has the potential to enhance the first step of the RCT pathway, promoting cholesterol efflux and the formation of nascent HDL. By recycling apoA-I back into the HDL fraction, the clearance of apoA-I is reduced and HDL levels are maintained [6]. HDL levels are dramatically reduced during inflammation, and HDL remodeling is significantly altered. The increased concentrations of acute phase proteins, both in the plasma and also incorporated on the HDL particle, could enhance the generation of lipid-poor apoA-I from HDL, altering the equilibrium between HDL-bound and lipid-poor apoA-I and generating more effluxing substrate. Although effluxing capacity is enhanced, with prolonged remodeling, these same particles are subject to enhanced catabolism.

The influence of acute phase proteins on HDL

During the acute phase response (APR) to infection, inflammation or trauma, cytokine-mediated changes in the composition of plasma proteins occur. HDL levels are dramatically reduced and HDL composition is altered. The synthesis of serum amyloid A (SAA) and group IIA secretory phospholipase A_2 ($sPLA_2$-IIA) in the liver is stimulated by circulating cytokines (IL-1β, IL-6, TNF-α) during the APR. SAA associates with HDL in plasma comprising the major apolipoprotein on HDL [7]. It was shown that SAA containing AP HDL is cleared faster and could contribute to the reduction in HDL levels [8], however SAA also has ABCA1 and SRBI-dependent cholesterol efflux capacity [9–10] that could promote the maintenance of plasma HDL. Endothelial lipase (EL) is another acute phase protein up-regulated during inflammation [11*] that preferentially hydrolyzes HDL phospholipids [12]. The hydrolysis of HDL by EL and $sPLA_2$-IIA may be partly responsible for the reduction in HDL levels during the APR [13–14]. The activity of phospholipid transfer protein (PLTP), which transfers phospholipids between different lipoproteins, is positively associated with SAA and C-reactive protein in patients with low HDL and cardiovascular disease [15]. In contrast, CETP levels and activity appear to be reduced during inflammation *in vivo* [16–17]. The mechanism for this reduction is not clear, although it was proposed that this was a compensatory mechanism to prevent further reductions in HDL during this state. CETP is a liver X receptor (LXR) target gene and up-regulation of CETP mass and activity was demonstrated in differentiated human macrophages (but not monocytes) exposed to LXR agonists [18*]. This up-regulation was maintained when macrophages were loaded with oxidized lipids. However, CETP up-regulation was abrogated by exposure to TNF-α or LPS. In contrast, the LXR-induced up-regulation of ABCA1 was not diminished by LPS. This

suggests that during inflammation, these changes to ABCA1 and CETP may assist in the maintenance of HDL levels by promoting cholesterol efflux and reducing HDL remodeling.

AP HDL remodeling *in vitro*

The physiological significance of AP HDL remodeling was addressed by Tam et al. [19*]. AP HDL isolated from mice was incubated with heparan sulfate *in vitro*. This resulted in the generation of apoA-I containing pre-β migrating particles that possessed cholesterol efflux capacity independent of lipase action. A role for SAA to enhance neutral cholesterol ester hydrolase activity and inhibit acyl-CoA:cholesterol acyltransferase activity was previously demonstrated [20]. The authors proposed that this action of SAA prevents the re-esterification of intracellular free cholesterol and combined with the effluxing capacity of the remodeled HDL, functions to promote cholesterol mobilization from lipid loaded macrophages.

Another recent study investigated the *ex vivo* properties of human AP HDL. In patients undergoing an APR, an increase in plasma SAA concentration and $sPLA_2$-IIA activity was associated with a reduction in CETP mass and activity [21*]. However, since CETP and HDL declined in concert, the CETP to HDL ratio was unaltered, suggesting that the ability of CETP to generate apoA-I from HDL may not be impaired during the APR. When the *ex vivo* efflux capacity of AP human plasma was measured, no attenuation of efflux was observed. This could also be attributed to the enhanced remodeling of HDL by $sPLA_2$-IIA during the APR, since *in vitro* remodeling of SAA-containing HDL by the combined action of $sPLA_2$-IIA and CETP generated lipid-poor apoA-I and SAA [21*] which have both been shown to have ABCA1-dependent efflux capacity [10]. Recent data demonstrate further close interactions between SAA and $sPLA_2$-IIA function in that SAA can up-regulate the $sPLA_2$ gene in smooth muscle cells via interacting with critical NF-kB and C/EBP sites [22**]. This suggests that SAA liberated from AP HDL during remodeling by $sPLA_2$-IIA and CETP could activate further expression of $sPLA_2$-IIA.

It is possible that remodeling of HDL by factors such as the co-expression of SAA and $sPLA_2$-IIA may be beneficial at local sites of inflammation by generating lipid-poor apoA-I. This could result in the mobilization of cholesterol from macrophages at sites of acute tissue injury as was mentioned for SAA above. However, in chronic situations such as rheumatoid arthritis or obesity, HDL levels may eventually become so reduced that there is a lack of “substrate” from which to derive lipid-poor apolipoproteins. For instance, when SAA and SRBI were over-expressed in mice, HDL were remodeled to smaller particles and this was associated with accelerated HDL catabolism [23*]. PLTP, like CETP, enhanced the remodeling of AP rabbit HDL *in vitro* [24]. As a consequence, more pre-β migrating apoA-I was generated, resulting in putatively enhanced efflux but with more rapid catabolism of the apoA-I. In comparison to normal HDL, PLTP-mediated remodeling of AP HDL liberated more pre-β migrating apoA-I that were prone to degradation. Proteolytic cleavage of apoA-I as a consequence of remodeling has not been shown for other lipases or transfer proteins, however this may, in part, underlie the enhanced catabolism of AP HDL.

HDL function during inflammation *in vivo*

Little is known about HDL remodeling in humans during the APR. Administration of a low dose endotoxin (2 ng/kg) to humans resulted in the induction of pro-inflammatory cytokines and SAA without reduction of HDL or apoA-I levels [25]. However HDL phospholipids declined. Neither CETP nor PLTP activity changed, providing indirect evidence that this may be due to the action of $sPLA_2$-IIA and possibly endothelial lipase. In fact, injection of lipopolysaccharide (LPS; 3 ng/kg) into human volunteers increased plasma EL levels. This co-incided with a decrease in both total plasma and HDL phospholipids [11*]. Over

expression of EL in mice markedly reduces plasma HDL-C [26] supporting the idea that EL activity contributes to the decreased HDL-C seen in inflammation. Although EL is primarily a phospholipase, it possesses some triglyceride lipase capacity [12]. Thus in the setting of inflammation-induced hypertriglyceridemia where HDL is enriched in TG, EL activity may be enhanced as it can act on both the surface and the core of AP HDL.

McGillicuddy et al. also observed minimal reductions in HDL and apoA-I in response to endotoxin (3 ng/kg) in humans, despite a large reduction in HDL phospholipids [27**]. Endotoxin treatment was associated with an increase in SAA expression and a reduction in efflux from macrophages to AP HDL. When macrophage to feces RCT was measured during sub-acute endotoxemia in mice, HDL cholesterol mass was unchanged during the APR. However, there was a reduction of cholesterol movement from macrophages to HDL. Furthermore, the capacity of HDL to promote cholesterol efflux *ex vivo* was impaired. A reduction in both ABCA1 and ABCG1- dependent cholesterol efflux to AP plasma was also shown in humans [21*]. However, when the *ex vivo* cholesterol efflux values were corrected to the acceptor concentration (apoA-I and HDL, respectively) which was also markedly reduced, cholesterol efflux was relatively maintained during the APR.

Anti-inflammatory effects of HDL

The anti-inflammatory properties of HDL, particularly on the endothelium have been extensively described [3]. However, the effects of HDL on monocytes are less well characterized. In a recent study, Murphy et al. showed that HDL potently inhibited expression of the integrin CD11b on the monocyte surface [28*]. They suggested that this interaction constitutes one mechanism for the anti-inflammatory effects. ABCA1 and cholesterol efflux *per se* constitutes another component as the anti-inflammatory effects were lost in monocytes derived from Tangier disease patients lacking ABCA1.

A direct anti-inflammatory role for ABCA1 was shown in macrophage-specific ABCA1 knock-out mice [29**]. In these mice, cholesterol efflux was attenuated. This was co-incident with a higher cell membrane free cholesterol and lipid raft content of macrophages. Furthermore, a hypersensitive response to LPS *in vitro* and *in vivo* was shown, which was dependent on a MyD88 pathway.

Recent evidence further links the interaction of HDL, particularly apoA-I with ABCA1 and ABCG1 as components of a pathway that could suppress inflammation. Mice lacking both ABCA1 and ABCG1 featured an “inflammatory” blood pattern characterized by increased neutrophils and monocytes, an increase in foam cell formation and accelerated atherosclerosis [30**]. This was attributed to an increase in cellular free cholesterol and enhanced signaling via Toll-like receptor 4.

Studies involving apoA-I Milano (apoA-I_M) emphasize the potential importance of ABCA1 and ABCG1 acting in an anti-inflammatory mode [31*]. Cimmino et al. showed that four days of treatment with this variant of apoA-I resulted in a significant reduction in the size and lipid content of aortas of rabbits fed a 0.2% cholesterol diet. A down-regulation of the inflammatory markers iNOS and caspase-3, as well as a reduction in atherosclerotic plaque oxidative stress was also observed. These changes were attributed to the anti-oxidant actions of apoA-I_M and its role in enhancing reverse cholesterol transport by virtue of up-regulation of hepatic and vessel wall ABCA1 and ABCG1. These results provide additional evidence that the combined effects of these transporters in mediating cholesterol efflux may in part account for the anti-inflammatory actions of HDL.

In other studies, Tang et al. showed that the interaction of apoA-I with ABCA1 rapidly activates JAK-2 and this enhances the interaction of apoA-I with the transporter [32–33].

Recent data shows that this interaction also activates STAT3, a transcription factor that was previously shown to have anti-inflammatory functions in macrophages [34**]. The interaction of apoA-I with cholesterol loaded macrophages suppressed LPS-induced production of inflammatory cytokines. Silencing STAT3 or ABCA1 in macrophages decreased the ability of apoA-I to inhibit cytokine production. Thus, the interaction of apoA-I with ABCA1-expressing macrophages activates a JAK2/STAT3 pathway that has anti-inflammatory activity. During inflammation, SAA is a major HDL apolipoprotein that interacts with ABCA1. Whether an SAA-ABCA1 interaction similarly activates anti-inflammatory pathways merits further study.

Chronic inflammation

The role that HDL apolipoproteins, particularly SAA, play in the low grade inflammation present in adipocytes in obese states merits consideration. King et al. [35*] demonstrated an up-regulation of SAA in apoE$^{-/-}$ mice with diet-induced obesity. The SAA associated with the pro-atherogenic lipoproteins VLDL and LDL and co-localized with biglycan and apoB in the sub-endothelial space. This contrasts with the situation during the APR when SAA mainly associates with the HDL fraction, suggesting that the lipoprotein class that SAA associates with may influence its function [35*]. Multi potent adipose-derived stem cells isolated from human adipose tissue secreted SAA in response to cytokines [36**]. Furthermore, SAA and ABCA1 were co-expressed in adipocytes with SAA enhancing cholesterol efflux from these cells compared with apoA-I. The degree to which the SAA in adipose tissue is derived from HDL or whether produced locally needs to be established.

Conclusions

The impact of inflammation on HDL is complex with numerous functional implications. In most species there is a reduction in HDL and apoA-I levels with a concomitant loss of anti-inflammatory potential. Enhanced remodeling likely results in the liberation of lipid-poor apoA-I that could enhance cholesterol efflux and therefore be athero-protective. At the same time, lipid-poor apoA-I is subject to rapid catabolism. The balance between these two processes may determine the net functional outcomes. The interaction of apoA-I with ABCA1, which is now recognized to promote anti-inflammatory responses, should be studied in the context of the APR.

Acknowledgments

The author acknowledges Drs Frederick C. de Beer, Nancy R. Webb and Deneys R. van der Westhuyzen for helpful comments in the writing of this review.

The work of the author was supported by an NIH Program Project Grant (PO1HL086670) to D.R. van der Westhuyzen.

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