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# HDL in Infectious Diseases and Sepsis

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## Abstract

During infection significant alterations in lipid metabolism and lipoprotein composition occur. Triglyceride and VLDL cholesterol levels increase, while reduced HDL cholesterol (HDL-C) and LDL cholesterol (LDL-C) levels are observed. More importantly, endotoxemia modulates HDL composition and size: phospholipids are reduced as well as apolipoprotein (apo) A-I, while

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serum amyloid A (SAA) and secretory phospholipase A2 (sPLA2) dramatically increase, and, although the total HDL particle number does not change, a significant decrease in the number of small- and medium-size particles is observed. Low HDL-C levels inversely correlate with the severity of septic disease and associate with an exaggerated systemic inflammatory response. HDL, as well as other plasma lipoproteins, can bind and neutralize Gram-negative bacterial lipopolysaccharide (LPS) and Gram-positive bacterial lipoteichoic acid (LTA), thus favoring the clearance of these products. HDLs are emerging also as a relevant player during parasitic infections, and a specific component of HDL, namely, apoL-1, confers innate immunity against trypanosome by favoring lysosomal swelling which kills the parasite. During virus infections, proteins associated with the modulation of cholesterol bioavailability in the lipid rafts such as ABCA1 and SR-BI have been shown to favor virus entry into the cells. Pharmacological studies support the benefit of recombinant HDL or apoA-I mimetics during bacterial infection, while apoL-1–nanobody complexes were tested for trypanosome infection. Finally, SR-BI antagonism represents a novel and forefront approach interfering with hepatitis C virus entry which is currently tested in clinical studies. From the coming years, we have to expect new and compelling observations further linking HDL to innate immunity and infections.

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**Keywords**

HDL • Infections • Bacteria • Parasites • Virus

## Abbreviations

ABCA-1	ATP-binding cassette transporter 1
ApoA-I	Apolipoprotein A-I
ApoE	Apolipoprotein E
ApoL-1	Apolipoprotein L-1
ApoM	Apolipoprotein M
IL-1 $\beta$	Interleukin-1 $\beta$
IL-6	Interleukin-6
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HDL-C	HDL cholesterol
LBP	LPS-binding protein
LCAT	Lecithin-cholesterol acyltransferase
LDL-C	LDL cholesterol
LPS	Gram-negative bacterial lipopolysaccharide
LTA	Gram-positive bacterial lipoteichoic acid
PAF-AH	Platelet-activating factor acetylhydrolase

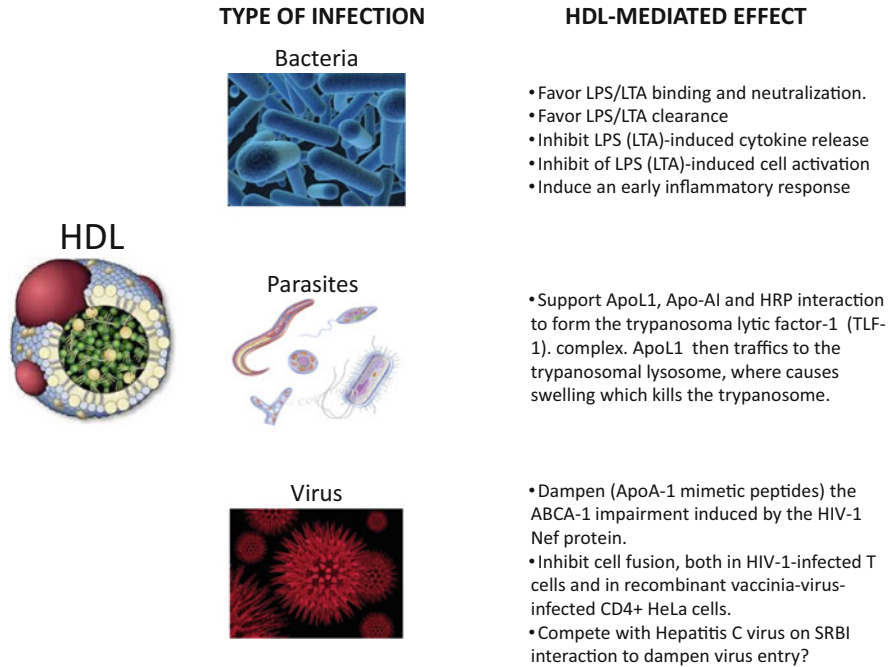
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PON1	Serum paraoxonase
PTX3	Pentraxin 3
rHDL	Reconstituted HDL
SAA	Serum amyloid A
S1P	Sphingosine-1-phosphate
sPLA2	Secretory phospholipase A2
SR-BI	Scavenger receptor class B member 1
TG	Triglycerides
TLF-1	Trypanosome lytic factor-1
TLRs	Toll-like receptors
TNF- $\alpha$	Tumor necrosis factor- $\alpha$

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## 1 Introduction

HDLs are heterogeneous particles generated by the continuous remodeling by lipolytic enzymes and lipid transporters and by lipid and apolipoprotein exchange with other circulating lipoproteins and tissues (Kontush and Chapman 2006). Mature HDL particles have a hydrophobic core containing cholesteryl esters and triglycerides, while proteins are embedded in a lipid monolayer composed mainly of phospholipids and free cholesterol. HDLs contain two main proteins, apolipoprotein A-I (apoA-I) and apoA-II, but several other minor apoproteins as well as enzymes such as lecithin-cholesterol acyltransferase (LCAT), serum paraoxonase (PON1), and platelet-activating factor acetylhydrolase (PAF-AH) are associated with HDL particles (Navab et al. 2004). HDLs possess several biological functions (Pirillo et al. 2013), but the role of HDL in innate immunity has emerged in the 1970s with the first observation associating HDL cholesterol (HDL-C) plasma levels to protection against sepsis. In the coming years, it has emerged that the ability of HDL to modulate cholesterol bioavailability in the lipid rafts, membrane microdomains enriched in glycosphingolipids and cholesterol, is evolutionary conserved and affects the properties of cells involved in the innate and adaptive immune response, tuning inflammatory response and antigen presentation functions in macrophages as well as activation of B and T cells. In the context of infections, HDL and their components have been linked with protection toward Gram-negative and Gram-positive bacteria and parasites, while the role during virus infection is debated (Fig. 1). Furthermore, HDLs influence humoral innate immunity by tuning the activation of the complement system and the expression of pentraxin 3 (PTX3). HDLs are critical not only during sepsis but also in other bacterial, parasitic, and viral infection. The aim of this chapter is to discuss the relevant findings on the link between HDL and immune response, shedding a new light on the role of these lipoproteins during sepsis and infectious disease.

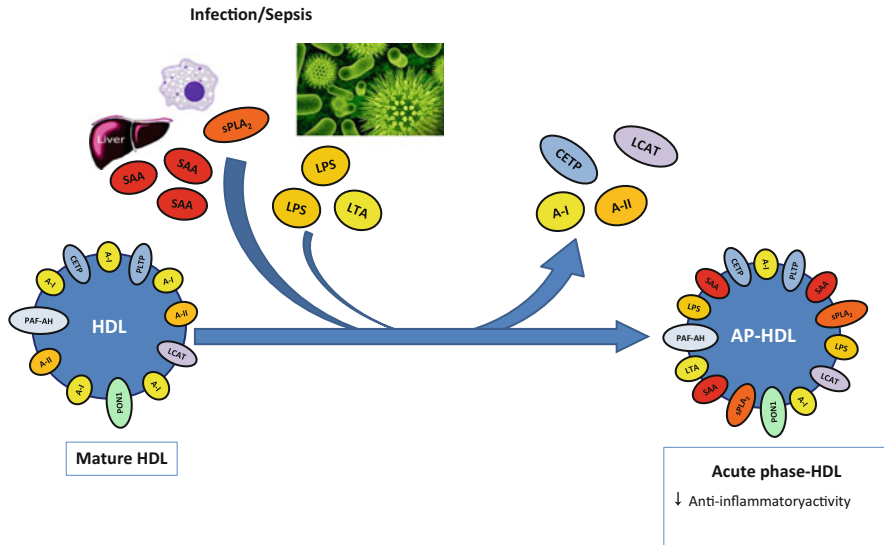


**Fig. 1** HDL and infections

## 2 HDL and Bacterial Infections

Increasing observations suggest that persistent low-grade inflammation is associated with the pathogenesis of severe chronic diseases such as atherosclerosis, diabetes, and other aging-related neurological diseases. Low levels of circulating Gram-negative bacterial endotoxin lipopolysaccharide (LPS) appear to sustain a non-resolving low-grade inflammation. As a consequence, low-grade endotoxemia may skew host immune environment into a mild non-resolving pro-inflammatory state, which eventually leads to the pathogenesis and progression of inflammatory diseases.

During infection, significant changes in the lipid metabolism are observed. At first, plasma levels of lipid and lipoproteins may change: triglyceride (TG) and VLDL cholesterol levels increase due to several mechanisms, including reduction of TG hydrolysis, LPS- and pro-inflammatory cytokines-induced de novo free fatty acid production, and TG synthesis in the liver and reduction of lipoprotein lipase activity thus resulting in reduced VLDL clearance and increased TG levels (Wendel et al. 2007). In addition, the increase in free fatty acids induces insulin resistance, thus contributing to increased glucose levels during systemic inflammation. On the other hand, HDL-C and LDL-C levels decrease during sepsis, and a low plasma



**Fig. 2** Acute-phase HDL

HDL-C level (associated with a low plasma apoA-I level) is a poor prognostic factor for severe sepsis, as it is associated with increased mortality and adverse clinical outcomes (Chien et al. 2005); more importantly, significant alterations in lipoprotein composition are observed, and increased levels of acute-phase proteins, including serum amyloid A (SAA) and secretory phospholipase A<sub>2</sub> (sPLA<sub>2</sub>), may contribute to decreased HDL-C levels, by replacing some structural and functional HDL components (Fig. 2).

Endotoxemia also modulates HDL composition and size: phospholipids are reduced while SAA dramatically increases and apoA-I decreases, and, although the total HDL particle number does not change, a significant decrease in the numbers of small- and medium-size particles is observed (de la Llera et al. 2012). The apoA-I content is reduced due to the rapid association of SAA, which displaces apoA-I and becomes the main protein of acute-phase HDL (Coetzee et al. 1986; Khovidhunkit et al. 2004); the content of other proteins associated with HDL (PON1, PAF-AH) is altered, resulting in reduced antioxidant properties of HDL (Feingold et al. 1998) and increased content of pro-atherogenic lipids (Cao et al. 1998; Memon et al. 1999). Also the lipid composition of HDL is altered during the acute-phase response (Khovidhunkit et al. 2004). Endotoxemia induces the increase of some enzymes involved in HDL remodeling, including endothelial lipase (Badellino et al. 2008) and secretory phospholipase A<sub>2</sub> (de la Llera et al. 2012), and the decrease of other, such as CETP and LCAT (de la Llera et al. 2012; Wendel et al. 2007). Altogether these changes result in the loss of functional properties of HDL (Banka et al. 1995; de la Llera et al. 2012; McGillicuddy et al. 2009).

## 2.1 Interaction of HDL with LPS and Gram-Negative Bacteria

Sepsis is a major cause of death in hospitalized patients. Mortality is mainly due to the cytotoxic actions of lipid components of the bacterial outer membrane. Lipopolysaccharide (LPS) is the toxic component of endotoxin in the outer membrane of Gram-negative bacteria. Lipoteichoic acid (LTA) is a heat-stable component of the cell membrane and wall of most Gram-positive bacteria that shares structural similarities with LPS and induces cytokine cascades alike LPS (Grunfeld et al. 1999).

LPS, the major pathogenic factor in Gram-negative sepsis, is an essential component of the bacterial cell wall, and it is not toxic when incorporated into the membrane; after release in the blood following bacterial cell reproduction, lysis, or death, lipid A, the most essential part of LPS, induces an inflammatory response (Van Amersfoort et al. 2003). This is mediated by pro-inflammatory cytokines released primarily from monocytes/macrophages and neutrophils, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), and interleukin-6 (IL-6) (Levine et al. 1993). LPS is recognized mainly by toll-like receptor 4 (TLR4) in cooperation with other proteins including MD-2, CD14, and LPS-binding protein (LBP) (Jerala 2007). LBP catalyzes the transfer of LPS to CD14, thus enhancing LPS-induced cell activation (Van Amersfoort et al. 2003). To prevent exaggerated responses to LPS, the host has developed several control mechanisms that include inhibitory LPS-binding proteins and plasma lipoproteins (Van Amersfoort et al. 2003).

In patients with severe sepsis, HDL-C decreases rapidly, and SAA is the major protein present in HDL (45 %) at the start of sepsis and is slowly replaced by apoA-I during recovery (van Leeuwen et al. 2003). Low HDL-C levels inversely correlate with the severity of septic disease and associate with an exaggerated systemic inflammatory response (Wendel et al. 2007), although it is difficult to establish whether changes in plasma lipoproteins simply reflect the severity of disease or they can directly modify the host response to inflammation. Also in healthy subjects low HDL levels are associated with increased inflammatory response on endotoxin challenge compared to subjects with normal or high HDL levels (Birjmohun et al. 2007), without differences in the HDL proteome (Levels et al. 2011). These observations indicate a positive role of HDL in the protection against sepsis.

Several mechanisms are involved in HDL-mediated protection. HDL, as well as other plasma lipoproteins (LDL, TG-rich lipoproteins), can bind and neutralize Gram-negative bacterial LPS as well as Gram-positive bacterial lipoteichoic acid (LTA) (Grunfeld et al. 1999; Murch et al. 2007). ApoA-I knockout mice, which lack HDL, exhibit decreased LPS neutralization in the serum compared with serum from control mice (Guo et al. 2013); overexpression of apoA-I moderately improves survival compared to controls, suggesting that HDL elevation may protect against septic death. In endotoxemic rats, in which LPS has been infused after HDL administration, HDLs attenuate LPS-induced organ damage accompanied by lower TNF- $\alpha$  and nitric oxide production (Lee et al. 2007). In addition to its role in LPS neutralization, HDLs exert its protection against sepsis also by promoting LPS clearance; in fact, almost all LPS exists in the

complex LPS–HDL in the blood (Ulevitch et al. 1979, 1981), the HDL receptor SR-BI binds and mediates LPS uptake, and HDLs promote SR-BI-mediated LPS uptake (Vishnyakova et al. 2003).

Administration of reconstituted HDL (rHDL) efficiently inhibits the LPS-induced cytokine release from the whole-blood system *in vitro* (Parker et al. 1995); however, the first study that demonstrated the LPS-neutralizing ability of rHDL in humans was performed by intravenous infusion of rHDL before induction of endotoxemia in healthy volunteers (Pajkrt et al. 1996). rHDL significantly reduced endotoxemia-induced inflammatory response, as it reduced clinical symptoms, reduced inflammatory cytokine (TNF- $\alpha$ , IL-6, IL-8) production, and attenuated LPS-induced leukocyte activation, in part due to the downregulation of the main LPS receptor monocyte-bound CD14 (Pajkrt et al. 1996). In LPS-challenged macrophages, HDLs selectively inhibit the activation of type I IFN response genes (Suzuki et al. 2010), which play a critical role in the antiviral response of cells, although emerging evidence also implicates this response in host defense during bacterial infection. This inhibitory effect of HDL does not require LPS binding to lipoproteins (Suzuki et al. 2010). HDLs (and apoA-I) attenuate also LPS-induced neutrophil activation (Murphy et al. 2011). More recently Di Nardo et al. (2014) have shown that HDLs promote the expression of ATF3 in macrophages, a transcriptional regulator which inhibits TLR2 expression. Of note the protective effects of HDL against TLR-induced inflammation were shown to be fully dependent on ATF3 *in vitro* and *in vivo*.

Another mechanism by which HDLs exert a protection against sepsis is by inducing an early inflammatory response to Gram-negative bacteria, thus helping to maintain a sensitive host response to LPS; HDLs exert this effect by suppressing the inhibitory activity of LBP (Thompson and Kitchens 2006). In contrast to native HDL, recombinant HDL did not increase cell response at early time points and are strongly inhibitory of cell response; this different effect is due to the composition of rHDL, which contain only apoA-I and PC and are optimized for LPS binding and neutralization (Thompson and Kitchens 2006).

Indeed apoA-I is a major HDL component that plays a central role in the anti-inflammatory functions of this lipoprotein class and exhibits protective effects against sepsis. ApoA-I in fact can directly inactivate bacterial endotoxin by protein–protein interaction (Emancipator et al. 1992), being the C-terminal half of apoA-I the main domain responsible for LPS neutralization (Henning et al. 2011), but also inhibits LPS-induced cytokine release from human monocytes (Flegel et al. 1993); in addition, apoA-I reduces TNF- $\alpha$  levels during LPS challenge in rats and increases the survival rates (Humphries et al. 2006), suggesting that apoA-I might inhibit LPS binding to macrophages thus inhibiting the production of inflammatory cytokines that are related to sepsis. In mice, the overexpression of apoA-I (that results in an increased serum level of both apoA-I and HDL) attenuates LPS-induced acute injury in lung and kidney (Li et al. 2008); LPS-induced pro-inflammatory cytokines decrease, as well as CD14 expression in liver and lung, resulting in a protective effect against systemic inflammation and multiple organ damage (Li et al. 2008). Similar to what reported in mice, subjects with low plasma

HDL levels (hypoalphalipoproteinemia) present an increased prevalence of classical CD14<sup>++</sup>/CD16<sup>-</sup> but not of intermediate CD14<sup>++</sup>/CD16<sup>+</sup> monocytes, further linking HDL- to LPS-mediated responses (Sala et al. 2013). Septic HDLs are almost depleted of apoC-I (Barlage et al. 2001). ApoC-I contains a consensus LPS-binding motif and is able to enhance the biological response to LPS thus reducing mortality in mice with Gram-negative-induced sepsis (Berbee et al. 2006). In fact, apoC-I binds to LPS and prevents its clearance by the liver and spleen, resulting in the stimulation of the LPS-induced pro-inflammatory response and protection against septic death (Berbee et al. 2006). These findings suggest that when LPS is released into the plasma following bacteria proliferation in the blood, apoC-I binds to LPS and presents it to responsive cells such as macrophages, leading to a rapid and enhanced production of pro-inflammatory cytokines, which are essential for effective eradication of the bacterial infection.

## 2.2 Interaction of HDL with LTA and Gram-Positive Bacteria

The effects of HDL on components of the bacterial outer membrane are not restricted to Gram-negative bacteria but also involve cell wall components of Gram-positive bacteria such as LTA which is able to induce an inflammatory response similar to that induced by LPS. Indeed it induces a massive production of mediators of inflammation that may result in systemic inflammatory response syndrome, septic shock, and multiorgan damage (Bhakdi et al. 1991; De Kimpe et al. 1995). LTA may also trigger disturbances of lipid metabolism, interfering with both lipoprotein production and lipoprotein clearance (Grunfeld et al. 1999).

All lipoproteins can bind LTA, but the majority of LTA is found in the HDL fraction (Levels et al. 2003), suggesting that HDLs have the highest affinity. In contrast to LPS, HDLs (as well as other lipoproteins) alone do not inhibit the cytokine production induced by LTA, but require the presence of lipoprotein-depleted plasma (Grunfeld et al. 1999), suggesting that lipoproteins contain cofactors in sufficient amounts to facilitate LPS binding to lipoproteins but not LTA binding. LBP is a plasma component (normally bound to HDL, but it can be found in lipoprotein-depleted plasma following ultracentrifugation) which enhances the activation of macrophages by LPS in the absence of lipoproteins and facilitates LPS binding to lipoproteins; LBP can also bind LTA (Tobias et al. 1989) and allows HDL to efficiently inactivate LTA (Grunfeld et al. 1999). The inhibition of LBP with neutralizing antibodies significantly decreases (53 %) the ability of lipoprotein-depleted plasma to facilitate LTA inactivation, but also suggests the presence of other plasma factors playing a role in HDL inactivation of LTA (Grunfeld et al. 1999).

ApoA-I has been shown to bind directly LTA *in vitro* and to attenuate LTA-induced NF- $\kappa$ B activation (Jiao and Wu 2008); apoA-I dose-dependently inhibits L-929 cell death induced by LTA-activated macrophages, and lipoprotein-depleted plasma strengthened this effect of apoA-I (Jiao and Wu 2008). In mice, apoA-I attenuates LTA-induced acute lung injury and significantly inhibits LTA-induced pro-inflammatory cytokine production (Jiao and Wu 2008).



These findings suggest that apoA-I can inhibit LTA activation by multiple mechanisms, by direct binding to LTA, and by interfering with LTA-mediated inflammatory response.

### 2.3 HDL and Mycobacteria

HDLs were reported to be protective also toward intracellular bacteria such as mycobacteria (Cruz et al. 2008). Intracellular pathogens survive by evading the host immune system and accessing host metabolic pathways to obtain nutrients for their growth. *Mycobacterium leprae*, the causative agent of leprosy, is thought to be the mycobacterium most dependent on host metabolic pathways, including host-derived lipids. Although fatty acids and phospholipids accumulate in the lesions of individuals with the lepromatous (also known as disseminated) form of human leprosy (L-lep), the origin and significance of these lipids remains unclear. Host-derived oxidized phospholipids were detected in macrophages within L-lep lesions, and one specific oxidized phospholipid, 1-palmitoyl-2-(5,6-epoxyisoprostanol E2)-sn-glycero-3-phosphorylcholine (PEIPC), accumulates in macrophages infected with live mycobacteria (Cruz et al. 2008). Mycobacterial infection and host-derived oxidized phospholipids both inhibited innate immune responses, and this inhibition was reversed by the addition of normal HDL, a scavenger of oxidized phospholipids, but not by HDL from patients with L-lep (Cruz et al. 2008). The accumulation of host-derived oxidized phospholipids in L-lep lesions is strikingly similar to observations in atherosclerosis, which suggests that the link between host lipid metabolism and innate immunity could contribute to the pathogenesis of both microbial infection and metabolic disease.

### 2.4 General Innate Host Defense Mechanisms Exerted by HDL After Bacterial Infection

In addition to limiting LPS or LTA responses during infection, HDLs exert additional functions during the innate immune response. In normal plasma, about 5 % of HDL particles contain apolipoprotein M (apoM) which binds sphingosine-1-phosphate (S1P), an important bioactive lipid mediator known to be associated with HDL (Christoffersen et al. 2011). The inhibition of apoM production results in the decrease of HDL-C levels and changes in HDL size, subclass profile, and functions (Wolfrum et al. 2005); apoM is a negative acute-phase protein that decreases during infection and inflammation (Feingold et al. 2008); in patients with severe sepsis and systemic inflammatory response syndrome (SIRS), a leading cause of mortality in non-coronary intensive care units, apoM plasma levels decrease dramatically suggesting a reduction of the vasculoprotective effects of apoM and its ligand S1P, with a strong correlation between apoM decrease and the severity of disease (Kumaraswamy et al. 2012). It is still unclear whether apoM and S1P levels may have prognostic value and whether changes in apoM levels contribute to the pathogenesis of SIRS and septic shock.

Another key player during the immune response regulated by HDL is the long pentraxin 3 (PTX3). This protein belongs, together with the C-reactive protein (CRP) and other acute-phase proteins, to the pentraxin superfamily: soluble, multi-functional, pattern recognition proteins. Pentraxins share a common C-terminal pentraxin domain, which in the case of PTX3 is coupled to an unrelated long N-terminal domain (Bonacina et al. 2013). PTX3, which is the prototypic long pentraxin, was identified in the early 1990s, as a molecule rapidly induced by IL-1 in endothelial cells (ECs) or by TNF- $\alpha$  in both ECs and fibroblasts (Breviario et al. 1992; Lee et al. 1993). The protein presents a high degree of conservation from mouse to human (82 % identical and 92 % conserved amino acids) and is induced in a variety of somatic and innate immunity cells by primary inflammatory stimuli (Garlanda et al. 2005). PTX3 is a key player of the humoral arm of the innate immunity, and its physiological functions are associated with the recognition and binding to different ligands, including microbial moieties, complement components, and P-selectin. This protein plays also a key role in cardiovascular diseases including atherosclerosis (Norata et al. 2009, 2010). Similarly to short pentraxins, PTX3 recognizes the highly conserved pathogen-associated molecular patterns (PAMPs) expressed by microorganisms (Iwasaki and Medzhitov 2010) and binds a number of bacteria, fungi, and viruses. A specific binding has been observed to conidia of *Aspergillus fumigatus* (Garlanda et al. 2002), *Paracoccidioides brasiliensis*, and zymosan (Diniz et al. 2004), to selected Gram-positive and Gram-negative bacteria (Bozza et al. 2006; Garlanda et al. 2002; Jeannin et al. 2005), and finally to some viral strains, including human and murine cytomegalovirus and influenza virus type A (IVA) (Bozza et al. 2006; Reading et al. 2008). Both short pentraxin and PTX3 bind apoptotic cells and facilitate their clearance (Doni et al. 2012; Jaillon et al. 2009). Surface bound CRP activates the classical pathway of complement through interaction with C1q, thus leading to cell elimination (Nauta et al. 2003). Cell-bound PTX3 might favor the clearance of apoptotic cells (Jaillon et al. 2009; Poon et al. 2010) by enhancing the deposition of both C1q and C3 on cell surfaces (Nauta et al. 2003). On the contrary, when in the fluid phase, PTX3 interacts with C1q and dampens the deposition on apoptotic cells and the resulting phagocytosis by dendritic cells and phagocytes (Baruah et al. 2006; Gershov et al. 2000; Rovere et al. 2000; van Rossum et al. 2004). In addition to PTX3, C1q recognizes and binds to ficolin-2 and mannose-binding lectin (MBL), thus modulating the classical and the lectin pathways of complement activation (Bottazzi et al. 1997). The best described and characterized ligand of PTX3 is the first component of the classical complement system C1q (Bottazzi et al. 1997; Nauta et al. 2003); PTX3 interacts with the globular head of the protein (Roumenina et al. 2006) thus resulting in the activation of the classical complement cascade only when C1q is plastic immobilized, a situation that mimics C1q bound to a microbial surface. Anti-inflammatory molecules were shown to modulate PTX3 expression. Under inflammatory conditions, glucocorticoid hormones (GCs) induce and enhance the protein expression in fibroblasts but not in myeloid

cells (Doni et al. 2008). Also HDLs, which possess a series of vascular protective activities, induce PTX3 expression in endothelial cells (Norata et al. 2008). The latter mechanism requires the activation of the PI3K/Akt pathway through G-coupled lysosphingolipid receptors and is mimicked by sphingosine-1-phosphate and others S1P mimetics (Norata et al. 2008), physiologically present in HDL and responsible for some of the activities linking HDL to the immunoinflammatory response (Norata et al. 2005, 2012). In vivo, an increased expression of PTX3 mRNA was detected in the aorta of transgenic mice overexpressing human apoA-I, compared to apoA-I knockout mice, and plasma levels of PTX3 are significantly increased in C57BL/6 mice injected with HDL (Norata et al. 2008). These data suggest that some of the beneficial effects in immunity of HDL may result also from the modulation of molecules that act as sensors of the immunoinflammatory balance.

In summary, all the observations showing that the increase of HDL is associated with an attenuation of LPS-induced inflammatory response (Levine et al. 1993; van Leeuwen et al. 2003) strongly favor the hypothesis that raising plasma HDL may represent a therapeutic approach in the treatment of sepsis and its complications. The picture however is more complicated, and not only HDL quantity but also HDL quality/composition is critical. For instance, the increase in sepsis-related mortality of the ILLUMINATE trial observed in the torcetrapib (a cholesteryl ester transfer protein inhibitor, increasing HDL-C levels) arm (Barter et al. 2007) was unlikely due to a direct effect of torcetrapib on LBP or bactericidal/permeability increasing protein function nor to inhibition of an interaction of CETP with LPS (Clark et al. 2010). It is rather possible that changes in plasma lipoprotein composition despite increased HDL levels, or the known off-target effects of torcetrapib, such as aldosterone elevation, could have aggravated the effects of sepsis (Clark et al. 2010). Apolipoprotein mimetic peptides represent an emerging area of HDL therapy; the most effective apoA-I mimetic peptide is 4F, which has been shown to improve HDL quality/function (Sherman et al. 2010; White et al. 2009). 4F mimics also anti-inflammatory properties of HDL: in vitro, 4F inhibits the expression of pro-inflammatory mediators in LPS-treated cells by directly binding to LPS, thus resulting in the inhibition of LPS binding to LBP (Gupta et al. 2005). In endotoxemic rats, the administration of 4F after LPS injection results in the attenuation of acute lung injury and increased survival, probably due to the preservation of circulating HDL-C and the downregulation of inflammatory pathways (Kwon et al. 2012); 4F also prevents defects in vascular functions and is associated with a decrease in plasma endotoxin activity in rats (Dai et al. 2010) and improved cardiac performance in LPS-treated rats (Datta et al. 2011). These observations indicate that, by scavenging LPS, 4F may prevent LPS-induced release of pro-inflammatory cytokines and changes in HDL composition resulting in an effective reduction of clinical complications associated with sepsis. Although promising, future studies are warranted to translate these findings into the clinical setting.

### 3 HDL and Parasitic Infections

The connection between HDL and parasitic infections mainly relates on the ability of specific apolipoproteins, which circulate as part of the HDL3 complex, to limit *Trypanosoma brucei* or *Leishmania* infection. The most relevant apolipoprotein in this context is apoL-1 which was discovered in 1997 (Duchateau et al. 1997) and was shown to be a part of a primate-specific complex named trypanosome lytic factor-1 (TLF-1) that also contains apoA-I and haptoglobin-related protein as the main protein components. TLF-1 has lytic activity toward African *Trypanosoma brucei brucei* and renders humans and most other primates resistant to infection with this parasite causing endemic infections of African cattle. The *Trypanosoma* species *brucei rhodesiense* and *brucei gambiense*, however, are resistant to TLF-1 and cause sleeping sickness in humans. Sleeping sickness is fatal when untreated and thus is an important health problem in many African countries. The trypanosome lytic activity has been associated with apoL-1 (Vanhamme et al. 2003); the apoL-1-containing complex is taken up by *T. b. brucei* via a receptor that binds hemoglobin and haptoglobin-related protein (Hb-Hpr). ApoL-1 traffics to the trypanosomal lysosome, where the acidic pH causes a conformational change, leading to activation of anion channel function in the apoL-1 N terminus. Lysosomal swelling kills the trypanosome (Perez-Morga et al. 2005). Thus, apoL-1 confers innate immunity against this parasite (Wheeler 2010). Over time, *T. b. brucei* developed a virulence factor called SRA that can inactivate apoL-1 protein, although the cellular location of this interaction is unknown. These SRA-expressing trypanosomes evolved into *T. b. rhodesiense*, the etiologic agent that causes acute African sleeping sickness (Wheeler 2010). This discovery has now been used to engineer a potential fusion protein drug for treating sleeping sickness caused by *brucei rhodesiense* in human (Baral et al. 2006). The active component in the novel protein drug candidate is a recombinant apoL-1 where the C-terminal SRA-binding region of wild-type apoL-1 has been deleted. This truncated apoL-1 alone probably has low biological activity when injected into plasma due to competition with endogenous apoL-1 (~6 mg/l) for uptake by trypanosomes. To circumvent this problem and effectively target recombinant apoL-1 to trypanosomes, the SRA-resistant apoL-1 without the C-terminal sequences was fused with a fragment of a high-affinity camel antibody (designated nanobody) specifically recognizing conserved epitopes of variant surface glycoprotein on trypanosomes (Baral et al. 2006). In vitro, the recombinant apoL-1–nanobody specifically bound to trypanosomes and was capable of lysing them in vivo. When mice infected with *Trypanosoma brucei brucei* were treated with the apoL-1–nanobody fusion protein, the parasites were promptly cleared from the circulation.

Another trypanosomatida, *Leishmania*, is also targeted by apoL-1 (Samanovic et al. 2009). It is certainly possible that apoL-1 has broad innate immunity properties, shaping the relative frequencies of the *APOLI* alleles. Of note the chronic kidney disease (CKD)-associated G1 and G2 variants (Parsa et al. 2013) encode forms of apoL-1 that evade SRA and remain active against *T. b. rhodesiense*. This, and/or other biological effects, may have conferred a selective

advantage to G1 and G2 heterozygotes, causing a selective sweep. The contribution of apoL-1 to CKD could also be related to the HDL functionality (Baragetti et al. 2013) under specific immunopathological conditions such as those observed during CKD. Hence, HDL could represent the bridge between apoL-1 and CKD and should be taken into consideration when exploring the contribution of apoL-1 to the disease. The delineation of how primates in late evolution have exploited HDL to fight parasite infections highlights the need of investigations on other potential roles of plasma HDL beyond those in lipid metabolism and reverse cholesterol transport.

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## 4 HDL and Viral Infections

Changes in plasma HDL-C levels have been reported to occur also during infection with viruses including human immunodeficiency virus (HIV) and hepatitis C virus (HCV). Furthermore, proteins related to HDL life cycle, such as SR-BI, were shown to play a key role in HCV infection. So far HDLs were proposed to increase virus infection and inhibit virus neutralizing antibodies; however, recent findings are challenging previous data and proposing a more complicated picture based on the ability of virus to take advantage of HDL–lipid transfer activity in host cells. Most of the available evidences linking HDL to viral infection are available for HIV and HCV.

### 4.1 HIV Infection

HIV infects and depletes CD4 lymphocytes, resulting in immunodeficiency and a slowly progressive disease. HIV is associated with dyslipidemia, namely, hypocholesterolemia, low levels of LDL, and hypertriglyceridemia (Riddler et al. 2003; Shor-Posner et al. 1993). HIV infection is commonly associated also with hypoalphalipoproteinemia; however, it is unclear whether virion replication plays a causative role in these changes. Some data suggest that hypoalphalipoproteinemia in patients with HIV is likely to be secondary to HIV infection itself (Rose et al. 2006). Systemic inflammation has been shown to lower the antioxidant and anti-inflammatory activity by transforming HDL to a pro-oxidant, pro-inflammatory acute-phase HDL (Kelesidis et al. 2013; Norata et al. 2006). A small pilot study of HIV-1-infected individuals with suppressed viremia on combination antiretroviral therapy showed that oxidative stress and inflammation in HIV-1 are associated with a marked reduction of HDL antioxidant–anti-inflammatory activities. In vitro, these abnormalities were significantly improved by treatment with the apoA-1 mimetic peptide 4F (Kelesidis et al. 2011). HIV infection is associated with modified HDL metabolism redirecting cholesterol to the apoB-containing lipoproteins and likely reducing the functionality of reverse cholesterol transport (Rose et al. 2008). Of note, the HIV-1 Nef protein can impair ABCA1 cholesterol efflux from macrophages, thus supporting atherosclerosis. This viral inhibition of efflux was correlated with a direct interaction between ABCA1 and Nef (Fitzgerald et al. 2010; Mujawar et al. 2006). More recently it was shown that

Nef downregulates ABCA1 function by a posttranslational mechanism that stimulates ABCA1 degradation but does not require the ability of Nef to bind ABCA1 (Mujawar et al. 2010).

Not all data are however concordant on this, and although HDL cholesterol and pre $\beta$ 1-HDL were significantly lower in all HIV-infected groups ( $p < 0.05$ ), mean levels of apoA-I and the ability of plasma to promote cholesterol efflux were similar in treatment-naïve HIV-infected patients or in HIV-infected patients on long therapy break. Of note a positive correlation between apoA-I and levels of CD4+ cells was also observed ( $r^2 = 0.3$ ,  $p < 0.001$ ) (Rose et al. 2008). Furthermore apoA-I, the major protein component of high-density lipoprotein, and its amphipathic peptide analogue were found to inhibit cell fusion, both in HIV-1-infected T cells and in recombinant vaccinia-virus-infected CD4+ HeLa cells expressing HIV envelope protein on their surfaces (Srinivas et al. 1990). The amphipathic peptides inhibited the infectivity of HIV-1. The inhibitory effects were manifest when the virus, but not cells, was pretreated with the peptides. Also, a reduction in HIV-induced cell killing was observed when virus-infected cell cultures were maintained in the presence of amphipathic peptides. These results have potential implications for HIV biology and therapy (Srinivas et al. 1990).

An aspect debated is how much the HIV infection and/or treatment contribute to the changes in HDL-C levels. With highly active antiretroviral therapy (HAART) intervention, mortality due to HIV was greatly reduced (Madamanchi et al. 2002). However, there have been several reports of increases in cardiovascular complications in patients with HIV. It is now established that some HAART regimens cause severe dyslipidemia, characterized by high levels of TC and LDL-C, hypertriglyceridemia, and hypoalphalipoproteinemia (Riddler et al. 2003). This clearly pro-atherogenic lipoprotein profile is associated with a rise in the incidence of CAD (Depairon et al. 2001). The rate of inflammation predicts changes in HDL-C and apoA-I following the initiation of antiretroviral therapy and indeed in a subgroup of participants not taking ART at study entry who were randomized in the Strategies for Management of Antiretroviral Therapy (SMART) to immediately initiate ART (“VS group”) or to defer it (“DC group”); HDL-C and ApoA-I levels increased among VS participants ( $n = 128$ ) after starting ART compared to DC. The effect of starting ART on changes in HDL-C and apoA-I was greater for those with higher versus lower baseline levels of IL-6 or hsCRP indicating that the activation of inflammatory pathways could contribute to HIV-associated changes in HDL (Baker et al. 2011). Also non-nucleoside reverse transcriptase inhibitors (NNRTI), such as nevirapine (NVP), were shown to increase apoA-I production, which contributes to the HDL-C increase after introduction of NVP-containing regimens. In view of the potent anti-atherogenic effects of apoA-I, the observed increase was suggested to contribute to the favorable cardiovascular profile of NVP (Franssen et al. 2009). Also efavirenz, another NNRTI antiretroviral treatment, was associated with HDL particles with a better antioxidant function, i.e., with a higher PON-1 activity. The PON-1 activity of black patients is higher than that found in whites regardless of treatment suggesting that ethnicity should be taken into consideration when studying drug effects on PON-1 activity (Pereira et al. 2009).

Overall the available evidences suggest that HIV infection could be associated with modified HDL metabolism redirecting cholesterol to the apoB-containing lipoproteins and likely reducing the functionality of reverse cholesterol transport and promote atherosclerosis. Additional pro-atherogenic mechanisms could be associated with a decrease in the anti-inflammatory properties of HDL.

## 4.2 HCV Infection

HCV is a major cause of liver cirrhosis and hepatocellular carcinoma. Viral entry is required for initiation, spread, and maintenance of infection and thus is a promising target for antiviral therapy. HCV exists in heterogenous forms in human serum and may be associated with VLDL, LDL, and HDL which can shield the virus from neutralizing antibodies targeting the HCV envelope glycoproteins (Agnello et al. 1999; Hijikata et al. 1993; Nielsen et al. 2006; Thomssen et al. 1992). HCV binding and entry into hepatocytes is a complex process involving the viral envelope glycoproteins E1 and E2, as well as several host factors, including highly sulfated heparan sulfate, CD81, the low-density lipoprotein receptor, claudin-1, occludin, and receptor tyrosine kinases (Lupberger et al. 2011; Zeisel et al. 2011).

Also SR-BI which binds a variety of lipoproteins and mediates the selective uptake of HDL cholesterol ester (CE) as well as bidirectional free cholesterol transport at the cell membrane emerged as a critical receptor affecting HCV entry. SR-BI directly binds HCV E2 (Bartosch et al. 2003; Evans et al. 2007; Scarselli et al. 2002), but virus-associated lipoproteins, including apoB containing, also contribute to host cell binding and uptake (Dao Thi et al. 2012; Maillard et al. 2006). Moreover, physiological SR-BI ligands modulate HCV infection (Bartosch et al. 2005; Voisset et al. 2005; von Hahn et al. 2006), suggesting the existence of a complex interplay between lipoproteins (not only HDL), SR-BI and HCV envelope glycoproteins for HCV entry. Earlier studies using small molecule inhibitors indicated a role for SR-BI lipid transfer function in HCV infection and HDL-mediated entry enhancement (Bartosch et al. 2003; Dreux et al. 2009; Syder et al. 2011; Voisset et al. 2005). A human anti-SR-BI mAb has been reported to inhibit HDL binding, to interfere with cholesterol efflux, and to decrease cell culture-derived HCV (HCVcc) entry during attachment steps without having a relevant impact on SR-BI-mediated post-binding steps (Catanese et al. 2007, 2010). However, SR-BI mediates the uptake of HDL-C in a two-step process including HDL binding and subsequent transfer of CE into the cell without internalization of HDL; a novel emerging hypothesis suggests that the interference with SR-BI lipid transfer function may be relevant for both initiation of HCV infection and viral dissemination independently of HDL function (Zahid et al. 2013).

Indeed SR-BI has also been demonstrated to mediate post-binding events during HCV entry (Haberstroh et al. 2008; Syder et al. 2011; Zeisel et al. 2007). HCV-SR-BI interaction during post-binding steps occurs at similar time points as the HCV utilization of CD81 and claudin-1 suggesting that HCV entry may be mediated through the formation of co-receptor complexes (Harris et al. 2008; Krieger



et al. 2010; Zeisel et al. 2007). Also the SR-BI partner PDZK1 was shown to facilitate hepatitis C virus entry (Eyre et al. 2010).

These data suggest that SR-BI plays a multifunctional role during HCV entry at both binding and post-binding steps (Catanese et al. 2010). Furthermore the HCV post-binding function of human SR-BI can be dissociated from its E2-binding function. Murine SR-BI does not bind E2 although it is capable of promoting HCV entry (Catanese et al. 2010; Ploss et al. 2009), and SR-BI, although able to directly bind E2 and virus-associated lipoproteins, could play additional functions during HCV infection (Bartosch et al. 2003; Dreux et al. 2009; Zeisel et al. 2007).

Although the addition of HDL enhances the efficiency of HCVcc infection, anti-SR-BI antibodies and SR-BI-specific siRNA efficiently inhibited HCV infection independently of lipoproteins (Zeisel et al. 2007). In this context, the post-binding activity of SR-BI is of key relevance for cell-free HCV infection as well as cell-to-cell transmission and by using antibodies which do not inhibit HDL binding to SR-BI; it was observed that post-binding function of SR-BI appears to be unrelated to HDL interaction but to be directly linked to its lipid transfer function (Zahid et al. 2013). So far small molecules and mAbs targeting SR-BI and interfering with HCV infection have been described (Bartosch et al. 2003; Catanese et al. 2007; Syder et al. 2011). A codon-optimized version of this mAb has been demonstrated to prevent HCV spread in vivo (Meuleman et al. 2012), and ITX5061, a SR-BI inhibitor, is in clinical development as HCV entry inhibitor (phase I, <http://clinicaltrials.gov/ct2/show/NCT01560468?term=ITX+5061&rank=3>).

Despite this promising approach, some open questions remain. First, it has been shown in vitro that apoA-I is required for HCV production (Mancone et al. 2011) and that serum amyloid A has antiviral activities against HCV which are reduced when HDL are co-incubated with SAA (Lavie et al. 2006). Given the changes between apoA-I and SAA occurring in HDL during the acute phase (Norata et al. 2012), it is still unknown whether this mechanism could be the consequence of viral infection or may represent part of the immune response which HCV learned to escape. Second, as the inhibition of SR-BI represents one of the most promising targets for HCV infection, the potential side effects on the impairment of HDL function should be carefully evaluated. The new data showing that HCV infection does not require receptor-E2-HDL interactions, coupled with the observation that HCV entry and dissemination can be inhibited without blocking HDL-SR-BI binding (Zahid et al. 2013), open a novel perspective for the design of entry inhibitors interfering specifically with the proviral function of SR-BI.

## Conclusion

HDLs are emerging as a relevant player in both innate and adaptive immunity (Norata et al. 2011, 2012; Sala et al. 2012). HDL activities rely not only on the ability to modulate cholesterol availability in immune cells but also on the role of specific molecules shuttled by HDL. During infections and acute conditions, HDL-C levels decrease very rapidly, and HDL particles undergo changes that dramatically alter their composition and function. Whether this is the consequence of a humoral innate response aimed at scavenging lipid bacterial



**Table 1** HDL-related therapies and infections

	Compound	References
Endotoxemia/ LPS scavenging	Recombinant HDL	Parker et al. (1995), Pajkrt et al. (1996)
	ApoA-I mimetics	Gupta et al. (2005)
Parasites infections Trypanosoma Leishmania	ApoL-1– nanobody	Baral et al. (2006), Samanovic et al. (2009)
Hepatitis C virus entry	SR-BI monoclonal antibodies	Bartosch et al. (2003), Catanese et al. (2007), Meuleman et al. (2012), Syder et al. (2011)

products such as LPS from the circulation and driving them into the liver for catabolism and elimination is still debated. Experimental evidence in genetically manipulated animal models suggests, however, that alterations in HDL structure/composition are associated with poor prognosis following endotoxemia or sepsis, further supporting a protective role for HDL. The same is true for some parasitic infections, where the key player appears to be a specific and minor apolipoprotein of HDL—apoL-1. For viral infections, the landscape is more complicated; SR-BI was clearly indicated as a player favoring virus entry; however, it is not clear whether viruses, such as HCV, evolved to take advantage of the HDL–SR-BI interaction to entry liver cells as *in vitro* studies suggest or whether *in vivo* HDL can compete for the interaction between HCV and SR-BI. Further studies are warranted in this context. Despite this, proteins related to HDL physiology represent already a target in clinical development for infections, and SR-BI antagonism represents a novel and forefront approach to interfere with hepatitis C virus entry.

All the observations showing that the increase of HDL-C is associated with an attenuation of LPS-induced inflammatory responses strongly favor the hypothesis that raising plasma HDL may represent a therapeutic approach in the treatment of sepsis and its complications (Table 1). HDL-related therapies are of great interest also in the context of parasites and virus infections (Table 1). As of beginning of 2014, the research in the field of HDL and immunity is in its infancy compared to the body of data available for HDL and atherosclerosis. From the coming years, we have to expect new and compelling observations further linking HDL to innate immunity.

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