Cardiovascular Research (2014) **103**, 372–383
doi:10.1093/cvr/cvu150

SPOTLIGHT REVIEW

HDL in innate and adaptive immunity

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Received 1 April 2014; revised 21 May 2014; accepted 23 May 2014; online publish-ahead-of-print 15 June 2014

During infections or acute conditions high-density lipoproteins cholesterol (HDL-C) levels decrease very rapidly and HDL particles undergo profound changes in their composition and function. These changes are associated with poor prognosis following endotoxemia or sepsis and data from genetically modified animal models support a protective role for HDL. The same is true for some parasitic infections, where the key player appears to be a specific and minor component of HDL, namely apoL-1. The ability of HDL to influence cholesterol availability in lipid rafts in immune cells results in the modulation of toll-like receptors, MHC-II complex, as well as B- and T-cell receptors, while specific molecules shuttled by HDL such as sphingosine-1-phosphate (S1P) contribute to immune cells trafficking. Animal models with defects associated with HDL metabolism and/or influencing cell cholesterol efflux present features related to immune disorders. All these functions point to HDL as a platform integrating innate and adaptive immunity. The aim of this review is to provide an overview of the connection between HDL and immunity in atherosclerosis and beyond.

Keywords HDL • Immunity • Lipid rafts • Macrophages

This article is part of the Spotlight Issue on HDL biology: new insights in metabolism, function, and translation.

1. Introduction

Premature atherosclerosis represents one of the major causes of morbidity and mortality in patients with chronic autoimmune-mediated inflammatory diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and other rheumatic autoimmune disorders,[1,2] which often present with an increased frequency of traditional risk factors for cardiovascular disease (CVD) including hypertension, obesity, diabetes mellitus, and altered plasma lipid profile.[3–5] In addition to decreased lipoprotein levels, low-density lipoprotein cholesterol (LDL-C) and/or high-density lipoprotein cholesterol (HDL-C) plasma levels are frequently observed in pathological conditions associated with immune activation.[6] In the last 30 years, clinical and experimental evidence accumulated, indicating that HDL possesses a general host defence activity which relies on the ability to scavenge and limit endotoxin toxicity as well as to influence immune cell response by affecting cholesterol content in plasma membrane lipid rafts. These activities are coupled with the well-known ability of HDL to limit inflammatory responses during atherogenesis.[7]

In this review, we will discuss the link between HDL and the immune system focusing on the effects of this class of lipoproteins on humoral and cellular immunity.

2. HDL levels and function impact immune responses

Modifications of HDL metabolism and/or plasma levels in animal models and in humans have been associated with altered immune responses, including a worsened acute response following infections, but also bone marrow leucocytosis as well as autoimmune features.

2.1 HDL and infections

HDL are endowed with an innate host defence activity after bacterial infection, which includes limiting the pro-inflammatory activities of lipid components of the bacterial outer membrane such as lipopolysaccharide (LPS), the toxic component of endotoxin in the membrane of Gram-negative bacteria, or lipoteichoic acid (LTA), a component of the cell membrane, and wall of most Gram-positive bacteria[8] (*Figure 1*).

During sepsis, serum LPS neutralizing activity was lower in apolipoprotein A-I (apoA-I) knockout mice, a model of very low HDL-C levels, compared with control mice, resulting in an exaggerated inflammatory cytokine production.[9] On the contrary, apoA-I transgenic mice (with high HDL levels) had an increased survival rate compared with controls during sepsis,[9] suggesting a role for HDL in protecting against septic death. The ability of HDL to promote the interaction of LPS with LPS-binding protein (LBP) favours LPS clearance,[10,11] a process involving the HDL receptor scavenger receptor class B type I (SR-BI) which binds the HDL–LPS complex and mediates its clearance.[12] Additionally, HDL/SR-BI interaction has been proposed as a critical step in providing cholesterol to the adrenal glands for glucocorticoid synthesis; this process is most relevant under stress conditions such as sepsis. In SR-BI$^{-/-}$ mice a reduced ability to induce glucocorticoid-mediated thymocyte apoptosis[13] was also observed.

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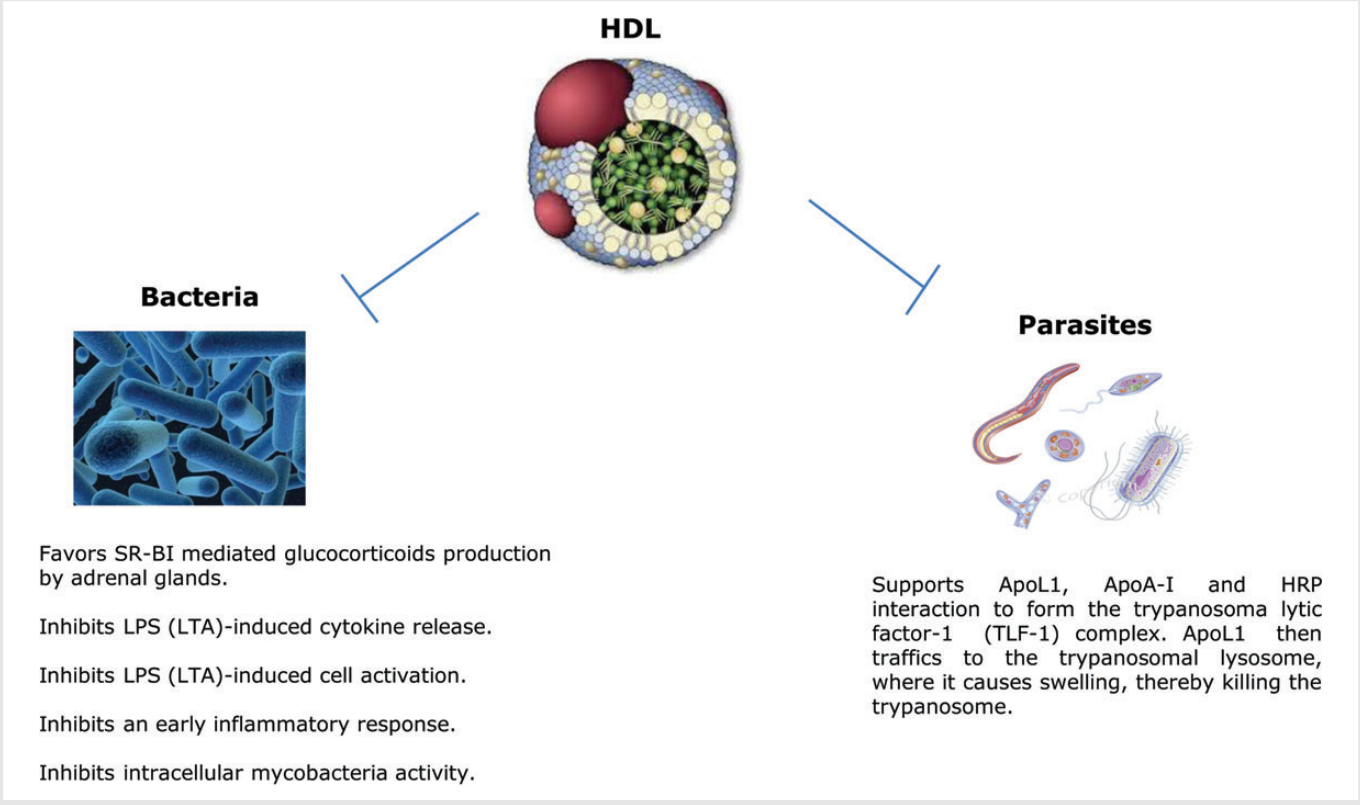

Figure 1 HDL and infections. HDL play a key role in dampening bacteria and parasite infection via several mechanisms.

In humans, low HDL-C levels inversely correlate with the severity of sepsis and an amplified systemic inflammatory response,[14] a relationship observed also in healthy subjects.[15] On the other hand, subjects with severe sepsis exhibit a rapid decline in HDL-C levels and function,[16] suggesting a key role for HDL in the protection against sepsis.

HDL protect also from infections by intracellular bacteria such as mycobacteria[17] (*Figure 1*). Both mycobacteria and host-derived oxidized phospholipids inhibit innate immune responses; HDL from healthy subjects, which act as scavenger of oxidized phospholipids, can revert this effect, while HDL from patients with leprosy, which are dysfunctional, do not,[17] suggesting a link between host lipid metabolism and immune function during infections.

Increasing plasma HDL-C levels by overexpressing human apoA-I resulted in lower cytokine levels and improved survival rates in transgenic mice challenged with LPS compared with mice with low HDL-C levels.[18] Similarly, administration of reconstituted HDL reduced LPS-induced inflammation in animals and humans,[19–21] suggesting that raising HDL might be a useful therapeutic approach for sepsis.

Changes in other specific apolipoproteins present in HDL such as apoL-1 are associated with susceptibility to parasite infections (*Figure 1*); apoL-1 is associated with a serum complex named trypanosome lytic factor-1 (TLF-1) that also contains apoA-I and haptoglobin-related protein.[22] TLF-1 has lytic activity towards African *Trypanosome brucei brucei* and confers resistance to this parasite in humans and most other primates.[23] After parasite infection, the apoL-1-containing complex is taken up by *T. B. brucei*; apoL-1 is then transferred to the trypanosomal lysosome, where it induces pore formation and lysosomal swelling, resulting in the lysis of the parasite.[24]

2.2 HDL deficiency and leucocytosis

HDL and its main apolipoprotein apoA-I promote cholesterol efflux from cells through different pathways, including the active cholesterol efflux via the ATP-binding cassette transporters ABCG1 and ABCA1, respectively.[25] Mice with combined deficiency of ABCA1 and ABCG1 exhibit very low HDL-C levels, a massive myocardial and spleen accumulation of inflammatory macrophage foam cells and, to a lesser extent, neutrophils in various tissues, including myocardium, lung, liver, spleen or thymus[26–29] similar to a classical myeloproliferative disorder.[30,31]

Of note, part of these effects were rescued when the impact of ABCA1 and ABCG1 deficiency was studied in apoA-I transgenic mice, characterized by increased apoA-I and HDL-C levels. These findings suggest a role for ABCA1, ABCG1, and HDL in the control of haematopoietic stem and multipotential progenitor cell proliferation.[31]

2.3 HDL deficiency and autoimmune phenotype

A direct link between low HDL-C levels and autoimmune disorders has been clearly established in animal models. $LDLR^{-/-}$ apoA-$I^{-/-}$ mice showed enlarged peripheral lymph nodes (LNs) and spleens, compared with $LDLR^{-/-}$ mice, with a high expansion of all classes of LN immune cells [(T and B cells, macrophages, dendritic cells (DCs)].[32,33] All these cells, but not macrophages, accumulated cholesteryl esters and developed an autoimmune phenotype.[32,33] These mice present also increased HDL particle diameter compared with $LDLR^{-/-}$ mice.[32,33] Subcutaneous injections of lipid-free apoA-I prevented LN enlargement and cholesterol accumulation, as well as activation and proliferation of lymphocytes.[32,33]

In mice with deficiency of SR-BI an increased proliferation of T and B lymphocytes and an imbalanced cytokine production in lymphocytes and macrophages were observed.[34] The accumulation of lymphocytes in SR-BI-deficient mice induced the development of a systemic autoimmune disorder, characterized by the presence of circulating auto-antibodies, deposition of immune complexes in glomeruli and infiltration of leucocytes in kidneys,[34] suggesting a role of SR-BI in autoimmunity. Furthermore, SR-BI-null mice exhibit abnormal, larger HDL particles with increased cholesterol content and alteration of associated proteins, thus resulting in a reduced inhibitory effect on lymphocyte proliferation.[35,36]

All together, these observations indicate a key role of HDL in infections and immune disorders; understanding how HDL-C levels and/or HDL functions may be altered and the molecular mechanisms by which HDL exert their effects will help to further clarify their role in these conditions.

3. Acute phase conditions and immune disorders promote HDL-C reduction and modify HDL composition and size

3.1 Acute phase conditions

During acute conditions, including infections and sepsis, apoA-I plasma half-life is reduced, therefore decreased HDL-C and apoA-I are observed.[16,37–41] Low HDL-C plasma levels represent a poor prognostic factor associated with increased mortality and adverse clinical outcomes in the case of endotoxemia and sepsis.[42]

Also HDL composition is affected under these conditions.[43,44] The profile of HDL remodelling enzymes changes with increased endothelial lipase[45] and secretory phospholipase A2 (sPLA2),[46] and decreased of cholesteryl ester transfer protein (CETP) and lecithin–cholesterol acyltransferase (LCAT).[14,46]

ApoA-I is displaced from HDL by acute phase proteins, including serum amyloid A (SAA) and sPLA2,[47,48] and this promotes apoA-I catabolism in the liver and kidney.[49] The decreased content of paraoxonase 1 (PON1) and the increased levels of platelet-activating factor acetylhydrolase (PAF-AH)[50–52] dampen the antioxidant capacity of HDL.

Altogether, these changes result not only in the reduction of plasma HDL-C and apoA-I levels[16,37,38] but also in the loss of HDL functional properties.[46,53,54]

Another key protein present in HDL which related to acute phase conditions is apolipoprotein M (apoM). Patients with severe sepsis and systemic inflammatory response syndrome (SIRS) exhibit significantly lower apoM plasma levels, which negatively correlated with acute phase markers.[55] ApoM levels are reduced also during infection and inflammation.[56] ApoM deficiency results in an altered distribution of HDL subclasses and function.[57] Of note, apoM can bind sphingosine-1-phosphate (S1P), an important bioactive lipid mediator present in HDL[58] and responsible for several HDL-mediated effects.[59–61] It is now becoming evident that changes in the axis apoM-S1P during acute phase response result in a further reduction of HDL protective properties.

3.2 Autoimmune disorders

Although it is well known that HDL-C levels are inversely related to CVD risk, the research is shifting towards the assessment of functional status of HDL rather than evaluating their plasma levels.[62] Decreased levels of HDL-C and PON1 activity have been described in SLE and RA patients, suggesting that chronic (auto) immune-mediated inflammation could induce specific alterations in lipoprotein metabolism.[63–65] Particularly, in SLE patients, this condition is known as 'lupus pattern' of dyslipidaemia and is characterized by increased VLDL and TG and decreased HDL-C levels.[66–69] Abnormal HDL, which are enriched in TG and depleted in cholesteryl esters (CE), result in attenuated antioxidative activity,[70] reduced anti-inflammatory effects,[71] and lower capacity to promote cholesterol efflux.[69,72] In a study of premenopausal women with SLE, changes in HDL subfractions have been reported including lower proportion of large HDL2b and significantly higher proportions of small HDL3b and HDL3c,[73] which have also been observed in dyslipidaemia.[74] Other studies failed to demonstrate changes in HDL-C levels, but observed an impairment of HDL functions associated with a pro-inflammatory phenotype in SLE and, to a lesser extent, in RA patients.[64] The possibility that these changes in composition and function towards a pro-inflammatory lipoprotein profile contribute to the accelerated atherosclerosis in SLE and RA patients is a hypothesis that deserves further attention.[64,65]

Also patients with type 2 diabetes mellitus, a clinical condition recently redefined as an autoimmune disease rather than just a metabolic disorder,[75,76] exhibit an impaired HDL metabolism and the presence of dysfunctional HDL.[77–79] Whether the immune-related activities of HDL have a role also in this context beyond the known metabolic functions is an intriguing hypothesis, which is so far supported by circumstantial observations.

Dyslipidaemia has also been observed in inflammatory bowel disease (IBD), a disorder characterized by mucosal immune system dysregulation, which leads to an inappropriate and sustained activation of intestinal mucosal inflammation; IBD includes both Crohn's disease and ulcerative colitis.[80,81] An enhanced atherosclerosis has been reported in patients with Crohn's disease and was associated with changes in HDL-C levels and HDL composition and function.[80]

Despite the extensive observation of altered HDL-C levels and lipoprotein composition in immune disorders,[82] whether HDL represent a bystander of the altered immune-inflammatory status or a key player is unknown. Defects in the handling of cellular cholesterol critically affect the function of immune cells, including lymphocytes.[83] Since autoimmune diseases are sustained by an impaired adaptive immune response, which is mainly related to a hyper-activation of T and B cells and impaired lipid metabolism, modulation of lipid content in membrane lipid rafts by HDL might impact immune cell activation,[84,85] as described in Section 5.

4. HDL proteins and lipids elicit immunomodulatory activities

HDL act as a reservoir for a series of proteins and lipids endowed with immunomodulatory activities, including lipid transfer proteins involved in the scavenging of LPS (LBP, phospholipid transfer protein [PLTP], CETP), apoproteins (apoA-I, apoE, apoL-1, apoM), and immunoactive lipids (S1P).

LBP is a plasma component (mainly associated with HDL) that binds LPS and, in the absence of lipoproteins, favours its transfer to CD14 receptors, resulting in immune cell activation. In the presence of lipoproteins, LBP facilitates the binding of LPS to HDL, resulting in its inactivation and transfer to the liver.[86]

PLTP is a member of LBP family[87] able to bind and neutralize LPS, resulting in the inhibition of LPS-induced cellular responses.[88,89] After LPS injection in mice, PLTP mass and activity are significantly reduced.[90] PLTP deficiency in mice is associated with the partitioning of LPS in non-lipoprotein fraction, increased LPS residence time, and increased inflammatory response.[91] PLTP activity is increased in post-surgery patients with systemic inflammation or severe sepsis compared with patients without signs of infection.[92] Finally, PLTP is a key factor in the maintenance of S1P content in HDL, as PLTP deficiency significantly reduced S1P content in HDL.[93] Like PLTP, also CETP shares structural similarities with LBP.[87] During systemic inflammation, a reduction in CETP activity has been reported;[94,95] on the other hand, CETP transgenic mice showed a reduced mortality following sepsis.[96] CETP activity decreased in post-surgery patients with systemic inflammatory response or severe sepsis compared with patients with no signs of local or systemic infection;[92] furthermore, in patients with severe sepsis, mean CETP levels decreased between hospital admission and day 3 of sepsis, with the higher variations in non-survivors than in survivors,[97] supporting the concept that CETP may play a protective role against sepsis.

ApoA-I is the main structural and functional apoprotein of HDL and plays a key role in the induction of cholesterol efflux from cells. The interaction of HDL or apoA-I with cells results in cholesterol depletion and disruption of intracellular signalling in specific membrane microdomains enriched in cholesterol and sphingolipids, named lipid rafts.[98,99] Their main role is the compartmentalization of molecules to form functional platforms for biological processes.[100,101] Several receptors with key immunological functions are localized within the lipid rafts, including toll-like receptors (TLRs)[102] and T- and B-cell receptors (TCR and BCR).[103,104] The lipid composition of rafts determines their function; modification of lipid raft composition can modulate raft-dependent signalling due to protein delocalization and alter immune cell biological functions. ApoA-I and HDL significantly decreased lipid raft abundance in monocyte plasma membranes due to a rapid cholesterol efflux;[98] the axis apoA-I/ABCA1[105] seems to be the major pathway involved in this effect, while the axis HDL/SR-BI or HDL/ABCG1[106] play a contributing role. For instance, apoA-I prevents CD40-mediated pro-inflammatory signalling by modulating the cholesterol content of lipid rafts via ABCA1-dependent cholesterol efflux.[107] Also apoE, a major apolipoprotein in HDL, regulates haematopoietic stem cell proliferation, monocytosis, and monocyte accumulation during atherogenesis in animal models.[108] ApoE was found to be present on the surface of haematopoietic stem and multipotential progenitor cells (HSPCs), in a proteoglycan-bound pool, where it acted in ABCA1- and ABCG1-dependent fashion to decrease cell proliferation.[108] Despite robust evidence in mice, no data are available on the impact of apoE on immunity in humans.

ApoL-1 is a protein associated with HDL particles which possess a pore-forming microbicidal activity, resulting in the lysis and death of trypanosome,[24] and thus represents the factor responsible for the trypanolytic activity of human serum. As described in Section 2, the presence of this apoprotein in HDL confers an anti-parasitic activity to HDL.

ApoM is a negative acute phase protein associated mainly with HDL and represents the carrier of S1P in HDL.[58] ApoM levels drastically decrease during the acute phase response[55] thus resulting in decreased concentrations of S1P, a bioactive lipid that impacts angiogenesis, lymphocyte trafficking, endothelial barrier function, and inflammation.[58] S1P is generated from plasma membrane sphingolipids and its expression is increased under inflammatory conditions.[109] Several observations have suggested that S1P mediates many of the athero-protective functions of HDL.[110] Extracellular S1P signals via 5 G protein-coupled receptors (S1PRs) that are differentially expressed in various subset of immune cells and their activation is involved in the control of immune cell trafficking.[109] The effects of S1P/S1P receptors activation on immune cells will be discussed in more detail in the subsequent section.

5. HDL and cellular immunity

Cell-mediated immunity involves the activation of several cell types; available data indicate that HDL can influence the activity of monocyte/macrophages, DCs, and lymphocytes mainly by modulating cholesterol content in lipid rafts and receptor activity, as well as by influencing immune cell activation (*Figure 2*).

5.1 Monocyte/macrophages

Monocytes play a major role in innate immunity as they can provide non-specific protection against foreign pathogens mainly through phagocytosis and production of cytokines. Two main subsets of monocytes exist, based on the relative expression of surface CD14 and CD16;[111] in addition, also chemokine receptors are differentially expressed by monocyte subsets.[111] A different prevalence of classical $CD14^{++}/CD16^{-}$ but not of intermediate $CD14^{++}/CD16^{+}$ monocytes was reported in patients with hypoalphalipoproteinemia.[112]

In vitro, incubation of monocytes with HDL reduces both CD11b expression and monocyte adhesion to endothelial cells;[98] a similar effect was observed with apoA-I,[98] suggesting that HDL and apoA-I may prevent monocyte activation and recruitment. Similarly, in neuthrophils, HDL and apoA-I significantly reduced CD11b expression, migration, and adhesion,[113] thus modulating neutrophil recruitment to inflamed tissues and further supporting the anti-inflammatory activity of HDL[114] (*Figure 3*).

Based on the different cytokines produced in the microenvironment, monocytes can differentiate into two different macrophage types, known as M1 macrophages, which represent the classically activated macrophages promoting inflammation, and M2 macrophages which are involved in the resolution of inflammation.[115] M1 macrophages, which are induced by Th1 cytokines, express most TLRs, and secrete several pro-inflammatory cytokines including IL-12, IL-6, IL-1β, TNFα, M2 macrophages are induced by Th2 cytokines, secrete IL-10 and TGFβ.[115] Several humoral factors may modify the balance between M1 and M2 phenotype; among them, in mice, HDL increased the expression of markers of M2 macrophages resulting in significant changes in the content and characteristics of monocyte-derived macrophages and in atherosclerotic plaque regression.[116] However, this result has not been confirmed in humans: HDL did not influence M2 alternative differentiation of primary human macrophages; furthermore, monocytes isolated from subjects with genetically determined low levels of HDL differentiated into M2 phenotype similarly to healthy subjects.[117] These discrepancies may result from inter-species differences, as HDL was shown to induce M2 markers in polarized murine macrophages which are not expressed by human macrophages. M2 polarization is also promoted by apoA-I and the apoA-I mimetic peptide 4F; this effect was mainly related to the up-regulation of the production of the anti-inflammatory cytokine IL-10[118] (*Figure 3*).

Differentiated macrophages express a number of recognition receptors involved in innate immunity, which allow macrophages to maintain surveillance mechanisms. Among them, TLRs play a key role in the macrophage-mediated mechanisms of immunity.[119] TLRs recognize several conserved pathogen-associated molecular patterns, including

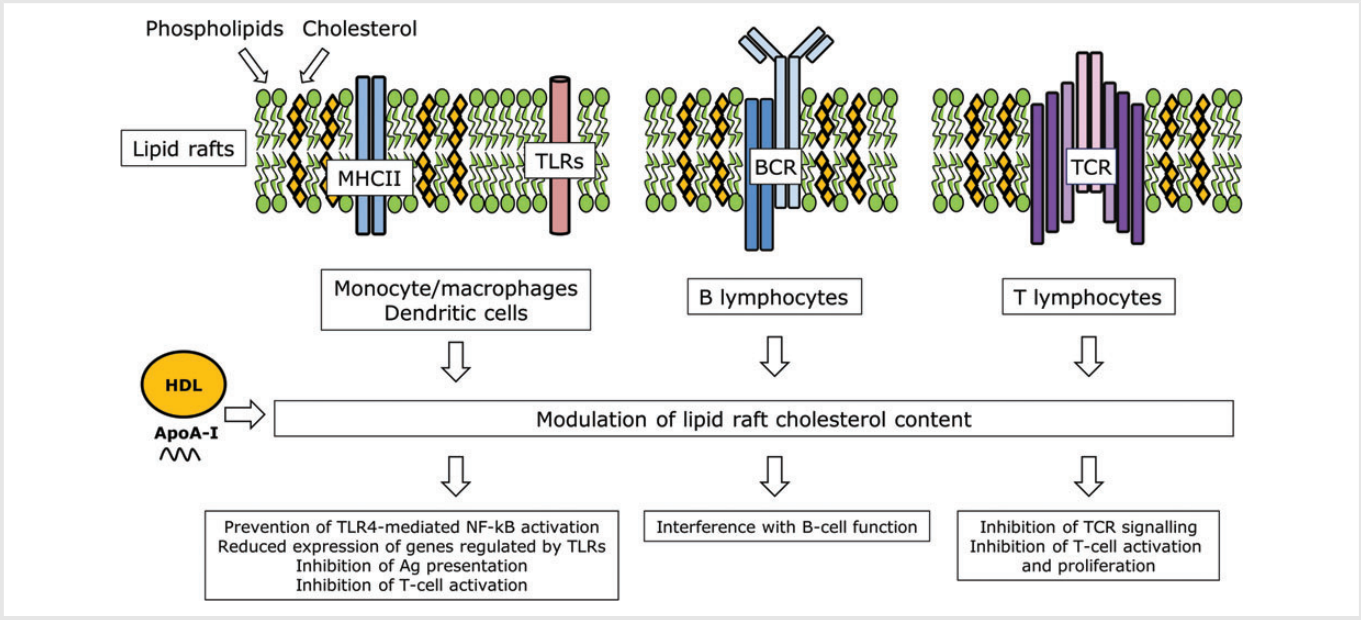

Figure 2 HDL modulate lipid rafts structure in immune cells. HDL and its main apolipoprotein (apoA-I) reduce cholesterol content in lipid rafts of several cell types, this results in the modulation of the function of key receptors involved in the innate and adaptive immune response.

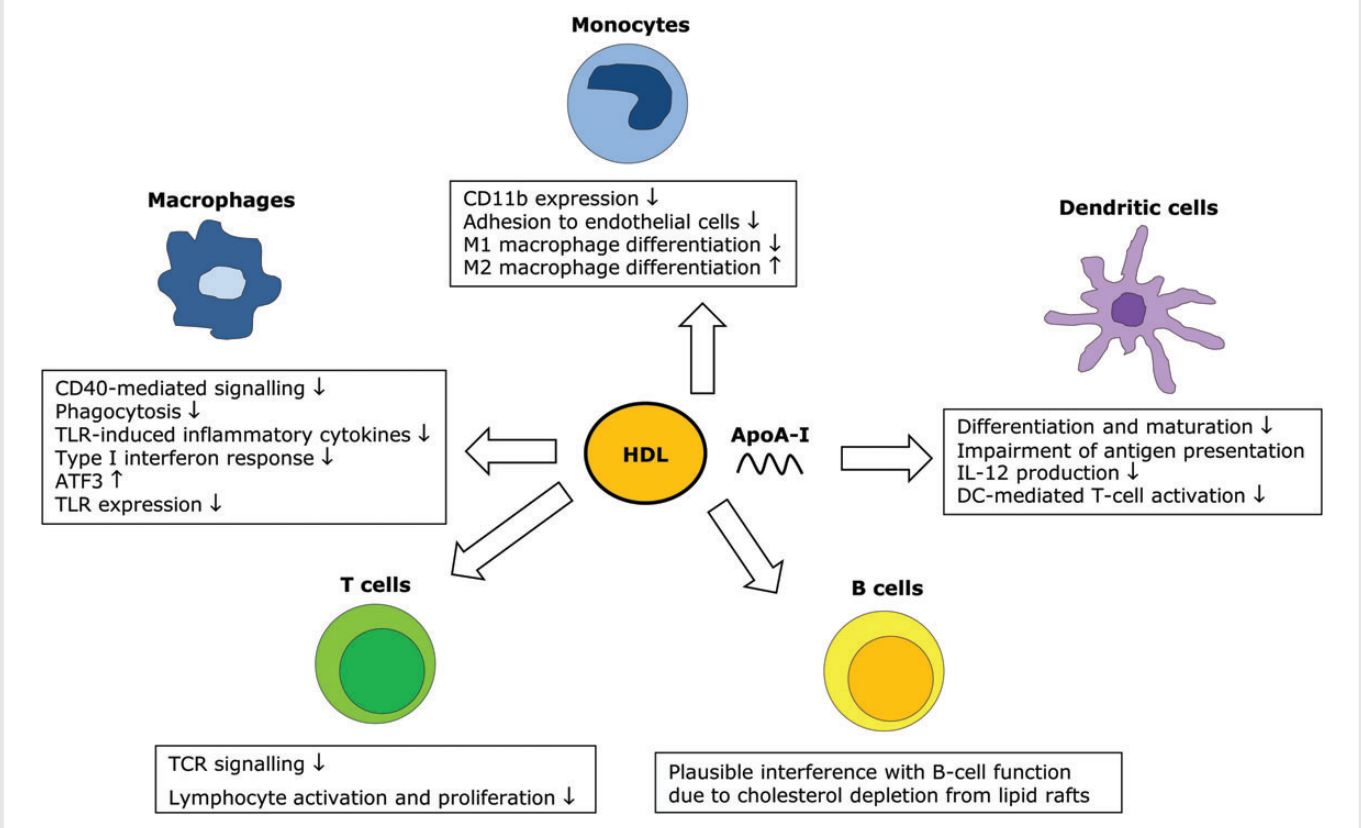

Figure 3 HDL- and apoA-I-mediated effects on immune cells. HDL modulate immune cells functions at different levels.

lipids, carbohydrates, peptides, and nucleic acids, and their association as heterodimers or the co-operation with other receptors allows the recognition of additional molecules.[119] After interaction with the ligand, either extracellular pathogens or endogenous ligand from damaged tissues, TLRs induce a signal transduction cascade that results in the modulation of a number of genes leading to the inflammatory

response.[120] Thus, when macrophages are challenged with the TLR4 ligand LPS, several hundred genes are upregulated; preincubation of cells with HDL prevented the activation of type I IFN response genes induced by LPS-mediated TLR4 activation, while no effect of HDL was observed in cells challenged with ligands of other TLRs.[121] Recently, the role of HDL in inhibiting TLR-induced pro-inflammatory cytokine expression at transcriptional level in macrophages has been elucidated.[122] The transcriptional regulator ATF3, which is induced following the stimulation of several TLRs, acts as negative regulatory transcription factor that limits TLR-induced inflammatory response, thus preventing the negative effects of an exaggerated innate immune response.[123] Incubation of macrophages with HDL increased the expression of ATF3, resulting in the reduction of TLR-induced pro-inflammatory cytokines.[123] In ATF3-deficient macrophages, this HDL-mediated effect was not observed.[122] These findings suggest that HDL may reduce the inflammatory response mediated by TLRs and that ATF3 might play a relevant role in this HDL-protective effect[124] (*Figure 3*).

TLR signalling is strictly dependent on cholesterol trafficking in rafts. In fact, macrophages lacking ABCA1 exhibit enlarged cholesterol-rich lipid rafts, with a higher content of TLR4 and an increased response to LPS stimulation;[125–127] similarly, an enhanced responsiveness to ligand of TLR2, TLR7, and TLR9, but not TLR3[127] is present in ABCA1 deficiency. Furthermore, ABCG1 or ABCG1/ABCA1 deficiency results in an enhanced response of macrophages to LPS, due to an increased cell surface expression of TLR4, despite no changes in the total amount of cellular TLR4;[28] also the response to ligands of other TLRs was increased.[28] These findings suggest that ABCA1 and ABCG1 play an anti-inflammatory role by suppressing the activation of TLRs and down-modulating the innate immune response. HDL and apoA-I, by promoting cholesterol efflux through ABCG1 and ABCA1, respectively, may contribute to control the innate immune response. In fact, apoA-I reduces the migration of TLR4 into lipid rafts, by depleting cholesterol from lipid rafts and thus preventing the TLR4-mediated NF-kB activation in endothelial cells.[128] Similarly, the apoA-I mimetic peptide 4F depletes cholesterol from lipid rafts and down-regulates cell surface expression of several TLRs in LPS-treated monocyte-derived macrophages, thus resulting in the down-regulation of genes modulated by the TLR signalling pathway[118,129] (*Figure 3*).

Abca1$^{-/-}$*Abcg1*$^{-/-}$ macrophages also present a reduced ability to protect against oxidized phospholipid-induced apoptosis and this effect is dependent on an excessive oxidative burst secondary to enhanced assembly of NADPH oxidase (NOX)2 complexes, which results in sustained Jnk activation and initiation of the apoptotic cell death programme.[130] Increased NOX2 assembly was dependent on an increased signalling via TLR4 (and to a lesser extent TLR2)/MyD88.[130] Of note, cholesterol efflux is critical for an efficient efferocytosis.

Also SR-BI is critical in the protection against nitric oxide (NO)-induced oxidative damage[131] and suppression of inflammatory cytokine generation in macrophages.[132] This suggests that part of the immunomodulatory effects of HDL might also be the consequence of the ability to limit the oxidative burst in immune cells.

S1P selectively attenuates TLR2 activation, resulting in the inhibition of TLR2-induced cytokine expression in macrophages.[133] Macrophages express mainly S1P1 and S1P2 receptors; S1P, through the action of S1P1 receptor, inhibited the LPS-induced production of pro-inflammatory cytokines in macrophages and resulted in the switch from a classical M1 pro-inflammatory to the M2 anti-inflammatory phenotype.[134] Of note, S1P, through the activity of S1P2 receptor, inhibits macrophage migration and recruitment to sites of inflammation.[135]

5.2 Dendritic cells

DCs are a heterogeneous family of bone marrow-derived immune cells specialized in the processing and presentation of antigens to T lymphocytes. After internalization of the antigen either by phagocytosis or by receptor-mediated endocytosis, DCs expose on their surface a fragment of the antigen bound to the major histocompatibility complex class II (MHCII), and simultaneously produce a co-stimulatory signal, resulting in the activation of T-cells and initiation of T-cell-mediated response.[136]

HDL and some of its components interfere with several steps of DC maturation and activity. ApoA-I impairs DC differentiation and maturation[137] by inducing prostaglandin E2 and IL-10, two known inhibitors of DC differentiation and function. HDL also significantly reduce the production of IL-12 (which favours T-cell differentiation towards Th1 subtype) in stimulated mature DCs, thus decreasing their ability to stimulate T-cells.[137] HDL may also interfere with DC maturation induced by TLR ligands; in fact, following TLR4 stimulation by LPS, HDL significantly inhibited the ability of DCs to induce a Th1 response of T-cells (characterized by the secretion of high levels of IFNγ), owing the reduced amount of IFNγ secreted compared with LPS alone[138] (*Figure 3*). Moreover, HDL reduced IL-12 production from LPS-stimulated DCs.[138] This effect of HDL is not restricted to TLR4, but extends also to other TLRs.[138] Among HDL components, the phospholipid fraction is the most active in inhibiting the functional DC maturation.[138]

Lipid rafts present in DCs are involved in the antigen presentation activity and in T-lymphocyte activation. In fact, MHCII molecules are localized within lipid rafts, thus resulting in the concentration of specific proteins in these highly specialized microdomains; this allows DCs to activate T-cells with very low amount of antigen.[139] As a consequence, disruption of DC lipid rafts results in the inhibition of antigen presentation and T-cell activation.[139] Both HDL and apoA-I inhibited the ability of DCs to activate T-cells and decreased IL-2 production; this effect was related to reduced membrane lipid raft content and reduced density of MHCII.[140] Cholesterol repletion restored IL-2 secretion and T-cell activation,[140] confirming the crucial role of cholesterol in the activity of antigen presenting cells.

Alterations in lipid raft composition may also influence the activity of 'lipid sensing' immune cells.[141] Among these cells, a key role is played by CD1-expressing antigen presenting cells as well as by natural killer T (NKT) cells which are CD1d-restricted lymphocyte T cells. Most of the available data suggest a pro-inflammatory and pro-atherogenic role for NKT cells in animal models;[142] however, the presence of different NKT subsets and the observation in humans that NKT cell levels are reduced in several immune disorders suggest a more complex picture.[141] Understanding CD1d-NKT cell biology in the context of immuno-metabolic disorders represents one of the challenges for the next years.

The activation of S1P receptors in DCs can influence their trafficking. S1P is a chemotactic factor for immature DCs as it stimulates cell migration, but this effect is lost in LPS-differentiated DCs.[143] Exposure of DCs to S1P reduces IL-12 and TNFα production and increases IL-10 secretion, thus resulting in an impaired ability to induce Th1 response while promoting Th2 response.[143] In addition, S1P differently regulates the production of some cytokines, reducing pro-inflammatory cytokines IL-12 and IL-23 secretion and increasing IL-27 production in LPS-stimulated DCs;[144] this effect was due to the activation of S1P1 receptor[144] and confirmed the anti-inflammatory properties of S1P in DCs.

5.3 Lymphocytes

Lymphocytes play a crucial role in immunity and lipid rafts are involved in lymphocyte activation.[103] In fact, T-cell receptor (TCR) and B-cell receptor (BCR) are integral membrane proteins localized within lipid rafts and their activity is strictly modulated by alterations in the lipid raft composition and structure.[6,103,104] Lipid rafts can regulate immune cell function by promoting proteins clustering; this may result either in the activation of the immune synapses or in a limited availability of membrane proteins involved in downstream signalling.[145] In addition, lysosphingolipids, components of lipid rafts, are involved in the lymph node/circulation trafficking of lymphocytes as well as in the differentiation of T-cell subsets.[146,147] Lipid rafts play an important role in BCR-mediated signal transduction; in the absence of stimuli, BCR is localized outside lipid rafts, but after receptor engagement by an antigen, BCR rapidly translocates into lipid rafts and initiates a signal transduction cascade.[104] The complex BCR-antigen is then internalized and the antigen processed to produce antigenic peptide that, in turn, are loaded onto MHCII and brought to membrane lipid rafts for antigen presentation to T cells.[104] The relevant role of lipid raft in B-cell activity is also supported by the observation that the Epstein–Barr virus (EBV), a virus with a tropism for B lymphocytes, targets B-cell rafts resulting in the disruption of BCR-mediated signalling and antigen transport functions;[148] the viral latent membrane protein 2A (LMP2A), in fact, is localized within lipid rafts and blocks the entry of BCR.[148] On the other hand, B-cells from patients with SLE have reduced levels of Lyn, a negative regulator of BCR-mediated signalling, and exhibit a decreased translocation to lipid rafts.[149] It appears reasonable that HDL may also interfere with B-cell function, although clear data are still lacking.

Alterations in cellular cholesterol metabolism were reported to critically influence LXR signalling which couples sterol metabolism to T-cell proliferation in the acquired immune response.[150] Mice lacking LXR beta show splenomegaly and lymphadenopathy and the activation of LXR beta signalling was reported to favour ABCG1 expression in T-cells thus limiting proliferation.[150] ABCA1 and ABCG1, two proteins involved in apoA-I- and HDL-mediated cholesterol efflux respectively, regulate haematopoietic stem cell proliferation and their deficiency result in leucocytosis and expansion of progenitor cell population in mice.[31] Furthermore, apoA-I prevents T-cell activation and proliferation in peripheral lymph nodes in mice fed an atherogenic diet by modulating cholesterol accumulation in lymph nodes.[32] Altogether, these observations further support the role of lipid rafts in the control of immune cell function. Also in patients with SLE, cholesterol availability in lipid raft play a key role in modulating T-cell function.[83] Further studies are required to understand whether a cross talk between SREBP and LXR pathways in T cells exist or whether the LXR pathway is activated to compensate for the dysregulation of other aspects of cholesterol metabolism in autoimmune cells. Of note, alterations in T-cell immunological synapse and increased expression of memory T-cell subsets occur in patients with coronary artery disease (CAD).[69,151,152] Moreover, T cells from synovial fluid of inflamed joints of patient with RA have an activated phenotype compared with peripheral T cells,[153,154] probably related to an ROS-mediated perturbation of proteins from lipid rafts.[155]

Lipid rafts are enriched in sphingolipids, a lipid class metabolized to ceramide which in turn generate sphingosine; the latter may be phosphorylated by sphingosine kinase (SPHK) to form S1P,[156] a bioactive lipid mainly associated with HDL.[58] Both S1P and SPHK play a relevant role in several inflammatory disease, including atherosclerosis, RA and asthma, most likely by modulating macrophage biology and function.[157] The activation of the lysosphingolipids receptors-PI3K/Akt axis by S1P or other S1P mimetics are responsible for the induction of several genes involved in the immune response including the long pentraxin PTX3 or the transforming growth factor beta 2 by HDL.[60,61] S1P plays a relevant role also in lymphocyte function. In fact, S1PR activation and the resulting signalling cascade facilitate the egress of T-lymphocytes from lymphoid organs,[146,158] and also control T-cell lineage determination.[147] In fact, S1P is a switch factor that inhibits the differentiation of regulatory T cells (Tregs) but drives differentiation of T helper type 1 cells (Th1).[147] On the other hand, administration of apoA-I to LDLR$^{-/-}$-apoA-I$^{-/-}$ mice reduces inflammation by inducing a significant increase of the Treg population and reducing the ratio effector/effector memory T cells.[33]

Also changes in the level of membrane ganglioside M1 (GM1), together with cholesterol, have been reported in activated and autoimmune lymphocytes;[84] CD4+ lymphocytes from SLE patients are characterized by increased levels of raft-associated glycosphingolipids (GSL) and cholesterol, defects in lipid raft location and function of key TCR signalling molecules, accelerated recycling of TCR-associated proteins, increased cell death and defects in mitochondrial function and autophagy.[84,85,159] Similarly, B-lymphocytes from SLE patients have a higher expression of GM1 which was accompanied by reduced expression of kinases involved in TCR signalling.[84,149] In line with these observations, the inhibitor *N*-butyldeoxynojirimycin (NB-DNJ), a successful, clinically approved therapy for patients with lysosomal storage disease (LSDs), normalized GSL expression and rectified some of the signalling and functional abnormal characteristic of T cells from SLE patients.[83]

Taken together, these observations suggest that molecules such as HDL which can influence lipid rafts composition might affect lymphocyte functions.

6. HDL as a therapeutic target for endotoxemia and immune disorders

In vitro, the administration of reconstituted HDL (rHDL) significantly lowered LPS-induced cytokine production,[160] and the intravenous infusion of rHDL before LPS administration in healthy volunteers resulted in a significant reduced inflammatory response.[20] HDL inactivate also LTA, the cell wall components of Gram-positive bacteria, which is structurally similar to LPS and induces cytokine cascades similar to those of LPS (*Figure 1*).[8]

In PG-polysaccharide (PG-PS)-induced arthritis in female Lewis rats, an experimental animal model of arthritis that has many features in common with human RA, intravenous infusions of lipid-free apoA-I or rHDL effectively reduce joint inflammation in this animal model by reducing inflammatory cell infiltration and inhibiting TLR2 expression and activation.[161] ApoA-I and rHDL mediate these effects by decreasing NF-κB activation in an ABCA1- and ABCG1-dependent manner in macrophages.[161] In the rat collagen-induced arthritis model, therapy with the apoA-I mimetic peptide D-4F combined with pravastatin significantly improved clinical disease, due to a reduction of inflammatory cytokines and chemokines.[162] Pravastatin or D-4F alone were not effective in controlling clinical arthritis activity.[162]

Treatment with the apoA-I mimetic peptide L-4F, in the absence or presence of pravastatin, effectively reduced manifestations of upus-like autoantibody production, glomerulonephritis, and

osteopenia in apoE$^{-/-}$Fas$^{-/-}$ B6 murine model of accelerated atherosclerosis in SLE.[163] In addition, despite enlarged aortic atheromas present in all treatment groups, analyses of plaque composition suggest a potential remodelling.[163] Indeed atherosclerosis and its clinical consequences are major contributors to morbidity and mortality in women with SLE.[163]

Therefore, targeting membrane lipids might be a novel approach to control or alter immune cell activation and may be an important therapeutic approach for autoimmune diseases. Statins are currently under investigation as potential immune-modulatory drugs: atorvastatin *in vitro* normalizes membrane GM1 expression, phosphorylation of intracellular kinases (LCK and ERK) and the production of IL-10 and IL-6 in T cells from SLE patients,[159] while in RA patients high dose of statin can modestly improve HDL functions.[164]

A study performed in patients with SLE treated with atorvastatin showed an improvement of T-cell signalling defects observed in these patients.[159] This observation suggested that atorvastatin might correct the function of auto-reactive T cells towards a tolerant phenotype probably by inducing changes in membrane lipids;[159] this hypothesis is supported by the association between persistence with statin therapy and reduced risk of developing RA reported in a large observational study.[165]

Although statins exhibit pleiotropic immunomodulatory effects *in vitro*[166] and in chronic and relapsing experimental autoimmune encephalomyelitis (an animal model of MS),[167] beneficial effects in MS patients are controversial showing both positive effects[168,169] and no advantages with statin treatment.[170,171] However, rHDL has been recently pointed as a target for the treatment of chronic inflammatory diseases:[172] rHDL has demonstrated to exert a direct immune-modulatory function on T-lymphocytes *in vitro* by suppressing their proliferation, decreasing the levels of IFNγ and IL-17 and modulating the induction of Th1 and Th17. Furthermore, studies in animal models indicate that increasing Treg levels induces a significant attenuation of atherosclerosis.[173,174] In humans, however, a significant inverse correlation between levels of HDL and Treg has been observed,[175] and circulating Treg levels do not correlate with severity of atherosclerosis.[175] The possible role of HDL in the polarization of T-lymphocyte subpopulations remains to be addressed as is the role of HDL therapies in the context of immune disorders.

7. Conclusions

HDL is emerging as a relevant player in both innate and adaptive immunity,[6,7,176] an effect mainly dependent on the ability to finely modulated cholesterol bioavailability in immune cell. However, additional beneficial immune-inflammatory effects of HDL could depend on the cargo of proteins and lipids carried by HDL which confer additional functions, such as the protection from endotoxemia or parasitic infections. The coming years will be critical to establish the role of HDL as a platform integrating humoral and cellular immunity and future studies should investigate the role of HDL in modulating innate and adaptive immune responses beyond atherosclerosis.

Conflict of interest: none declared.

Funding

G.D.N. is supported by Telethon Foundation GGP13002 and by Piano Sviluppo B-2013, University of Milan.

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