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Review

High-density lipoproteins and immune response: A review

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ABSTRACT

High-density lipoproteins (HDLs) are heterogeneous lipoproteins that modify their composition and functionality depending on physiological or pathological conditions. The main roles of HDL are cholesterol efflux, and anti-inflammatory and antioxidant functions. These functions can be compromised under pathological conditions. HDLs play a role in the immune system as anti-inflammatory molecules but when inflammation occurs, HDLs change their composition and carry pro-inflammatory cargo. Hence, many molecular intermediates that influence inflammatory microenvironments and cell signaling pathways can modulate HDLs structural modification and function. This review provides a comprehensive assessment of the importance of HDL composition and anti-inflammatory function in the onset and progression of atherosclerotic cardiovascular diseases. On the other hand, immune cell activation during progression of atheroma plaque formation can be influenced by HDLs through HDL-derived cholesterol depletion from lipid rafts and through HDL interaction with HDL receptors expressed on T and B lymphocytes. Cholesterol efflux is mediated by HDL receptors located in lipid rafts in peripheral cells, which undergo membrane structural modifications, and interferes with subsequent molecules interactions or intracellular signaling cascades. Regarding antigen-presentation cells such as macrophages or dendritic cells, HDL function may then modulate lymphocytes activation in immune response. Our review also contributes to the understanding of the effects exerted by HDLs in signal transduction associated to our immune cell population during chronic diseases progression.

1. Introduction

The association of high-density lipoprotein-cholesterol (HDL-C) with decreased risk of cardiovascular disease (CVD) is well established [1]. However, recent randomized controlled trials showed that HDL-C raising therapies did not lead to CVD protection [2]. Rather, HDL quality was found to correlate highly with the risk of CVD [3]. The lack of effect of HDL therapies has brought into question the role of HDL-C as a pharmacological target to reduce CVD risk [4–6]. However, HDL is a complex population of heterogeneous lipoproteins demonstrated to present antioxidant, anti-inflammatory [7] and anti-apoptotic properties—HDLs can inhibit apoptosis in endothelial cells [8]. HDL anti-inflammatory and antioxidant functions are considered to influence CVD risk [9]. This has led to the hypothesis that improving HDL function may be more relevant for CVD protection than raising HDL-C level [2]. Additionally, HDL particle size has been associated to CVD risk, small HDLs increase CVD risk [10,11].

HDL cholesterol efflux capacity (CEC) is the most studied HDL function because CEC is the first step in reverse cholesterol transport (RTC). CEC is suggested to be a better biomarker of HDL-related CVD protection than HDL-C [12,13]. In addition, when HDL-C was carried by small HDLs, coronary artery disease (CAD) risk was found to decrease [14], suggesting that not only HDL size distribution is important for HDL-associated CVD protection, but also HDL composition distribution among different particle sizes.

Atherosclerosis remains the main cause of CVD. Atheroma plaque formation is surrounded by a repeated inflammatory reparative reaction, where several mediators interact. Evidence shows a specialized immune response involved in the progression of atheroma plaque formation [15]. HDLs suppress cytokine and chemokine production in monocytes, macrophages and monocyte-derived dendritic cells, down-regulating costimulatory molecule production and antigen presentation [16]. In one of the first stages of atheroma plaque formation, oxidized low-density lipoproteins (ox-LDLs) are engulfed by macrophages and deposited in the intima. LDL oxidation can be prevented by functional HDLs, as HDL antioxidant function prevents oxidation of HDLs

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themselves [17]. However, in pathological conditions, HDLs oxidize and contribute to atheroma plaque formation. Oxidized HDLs are also less functional in such conditions [18,19].

Recent evidence reveals that dysfunctional or even pro-atherogenic HDL is generated during inflammation [20]. HDL composition changes as a result of inflammation, and inflammation-related molecules, such as serum amyloid A1 (SAA1), are incorporated into HDL [21]. HDLs are dysfunctional during inflammation, and CEC, anti-inflammatory and antioxidant functions are reduced during the acute phase [20].

The HDL family is diverse, with HDL types varying in size and protein and lipid composition. Traditionally, HDL-associated proteins have been considered to determine HDL structure and functionality [22]. For example, paraoxonase 1 (PON1) is an HDL-related antioxidant enzyme, which can develop other functions related to lipoprotein metabolism [23]. However, the lipid component in HDL has an important role in HDL function. Sphingomyelin 1 phosphate (S1P) is the most studied HDL-associated lipid, and negatively correlates with the overall severity of CAD [24] and with functional endothelial damage in sepsis [25]. In addition, plasmalogens demonstrate an inverse association with both stable and acute CAD, possibly reflecting a direct anti-apoptotic effect [26].

Taking into account the role of inflammation on HDLs—and vice versa—the aim of this review was to give an overview of HDL remodeling during inflammation and HDL influence over lymphocyte activation.

2. HDL and inflammation

2.1. HDL anti-inflammatory function

It is well recognized that HDL's role in CVD prevention depends on a set of HDL-associated functions. The HDL inflammatory index (HII) has been proposed to quantify HDL anti-inflammatory function in vitro and measures the functional ability of HDLs to modulate LDL oxidation. Higher HII (0.5–1) is associated with increased risk of CVD [9]. HII is closely related to HDL composition because HDLs carry oxidized lipids to their degradation [27], and HDLs comprise different proteins with antioxidant capacity (Table 1) [28]. In addition, HDLs bind lipopolysaccharides (LPS) in a process that highly depends on apolipoprotein A1 (apoA1) structure. HDL binding to LPS is associated with a reduction of systemic pro-inflammatory cytokine levels [29]. Although a change in the composition of HDLs during the acute inflammatory response decreases their anti-inflammatory capacity, it has been proposed that HDLs can regulate inflammasomes—multiprotein complexes assembled in the cytosol that induce the maturation of pro-inflammatory cytokines such as interleukin (IL)-1β and IL-12 [30,31].

Other important components in the inflammatory response are Toll-like receptors (TLRs) involved in the formation of atherosclerotic lesions [32]. HDL anti-inflammatory function is also highly related to CEC. It has been demonstrated that macrophage cholesterol accumulation amplifies TLR signaling, and thus, functional HDLs can reduce TLR signaling. TLRs are not constituents of lipid rafts but once activated, the TLRs will localize in lipid rafts for intracellular signaling [33]. However, the changes in lipid raft composition exerted by apoA1 lead to a reduction of the expression of some TLRs and the genes induced by them [34]. However, apoA1 has been described as an activator of TLR, inducing pro-inflammatory signals [35], and HDL may increase protein kinase C (PKC) activity, consequently inducing TLR signaling [36].

Another route by which HDLs have been found to modulate the function of TLRs is the activation of the transcriptional regulator ATF3 [16]. Using this approach, HDLs can modulate the function of TLRs by altering the microdomains, avoiding the migration of TLRs to lipid rafts and the subsequent activation of the signaling pathways, or by modulating negative regulator signs and decreasing the inflammatory process.

HDLs were also found to induce an inhibitor of TLR/nuclear factor kappa-light-chain enhancer of activated B cell (NF-κB) signaling and to impair induction of type I interferon downstream signaling [37]. Moreover, it has been demonstrated that HDLs and apoA1 act in an anti-inflammatory manner via induction of autophagy and recruitment of phosphorylated IkB kinase (p-IKK) to the autophagosome compartment, thereby preventing further NF-kB activation and induction of cytokine expression [38].

Table 1
HDL antioxidant proteins.

Protein	Antioxidant function	
PON1	Lactonase, thiolactonase, arylesterase and alryldialkylphosphatase	Protects LDLs and HDLs from oxidative damage
ApoA1	LPS binding	Reduce cytokine production
LpPLA2	Hydrolysis of short-chain oxidized phospholipids	Protects LDLs and HDLs from oxidative damage
GSPx-3	Hydroperoxides reduction	Protects LDLs and HDLs from oxidative damage

PON1, paraoxonase 1; ApoA1, apolipoprotein A1; LpPLA2, lipoprotein-associated phospholipase; GSPx-3, glutathione selenoperoxidase 3.

2.2. HDL remodeling during inflammation

HDLs are widely remodeled during inflammation. For example, during an inflammatory process, a reduction of cholesteryl esters and an increase in free cholesterol content were found. The decrease of cholesteryl esters may be explained by a reduction of lecithin cholesterol acyl transferase (LCAT) activity, associated with pathological conditions that are highly related to inflammation [39]. In addition, the protein content of HDLs is modulated during inflammation, together with a decrease in apoA1 and the inclusion of inflammatory cargo, such as SAA1 and complement C3 [40]. A negative correlation between HDL levels and other components of the complement cascade, such as C5b-C9 [41], has been described, suggesting that the membrane attack complex can be inhibited [42]. Moreover, HDL-associated enzyme activities are modulated, and lower LCAT and PON1 activity are described [39,43].

It is hypothesized that SAA1 replaces typical HDL proteins, such as apoA1, PON1 and apoM. Although the role of SAA1 is not clear, the main problem is the replacement of HDL functional proteins such as the S1P binding proteins [44] and apoA1, which interact with a variety of receptors and are essential for CEC development [45].

2.3. HDL properties and physiological conditions: sex and age

Not only pathological conditions, as inflammation, change HDL properties, but also different physiological conditions or processes influence HDL composition and properties, such as sex and aging.

The hormone profile in women modify HDL quantity, composition and size, specifically, female sex hormones are directly associated with HDL. Estradiol increases HDL particle number and follicle-stimulating hormone (FSH) shows the opposite role, as HDL size distribution and composition change depending on the predominant hormone. In particular, estradiol increases large HDL number and HDL phospholipid content, which are related to an improved CEC [46]. In addition, the antioxidant capacity of HDLs differ between sex, specifically, both arylesterase and lactonase activities of PON1 were significantly higher in women compared to men [47], differences which could be driven by hormonal differences that compromises HDL structure and PON1 anchoring and functionality.

Aging is a physiological process in which CVD risk increase. Lipoprotein quality is lower in the elderly [48], specifically HDL show reduced CEC [49] and PON1 activity [50] and a reduced capacity to prevent LDL and its own oxidation [48,50]. Additionally, during menopause transition, women experience a decline of estradiol level that would contribute to worsen HDL quality in women [51].

3. HDL signaling function

HDLs interact with a range of cell receptors and activate different pathways or be internalized, however, HDL internalization is poorly described [52]. ApoA1 is the main ligand of HDL-associated molecules but other HDL components, such as S1P, can also interact with cell receptors.

For example, HDL presents the ability to inhibit apoptosis in endothelial cells by activation of the Akt/eNOS pathway, activated by apoA1 and S1P by binding to its receptors SR-BI and S1P-2, respectively. This pathway inhibits the induction of apoptosis by the intrinsic pathway, helping maintain the endothelial integrity [53].

3.1. Scavenger receptor type 1

SR-BI remains the primary HDL receptor, promoting bi-directional cholesterol movement between cells and HDLs without degrading HDLs [54]. Other lipoproteins can interact with SR-BI, but the interaction with HDLs is more efficient [55]. In addition, several HDL types can interact with SR-BI, but the main interaction occurs with phospholipid-rich HDLs [56]. HDL's main SR-BI ligand is apoA1, an apolipoprotein that is recognized by SR-BI (Fig. 1) [57].

HDL-SR-BI interaction produces SR-BI dimerization [58] and SR-BI induces the activation of three protein kinases: src [59], liver kinase B1 (LKB1) and calcium calmodulin-dependent protein kinase (CAMK) [60]. Src phosphorylation activates phosphatidylinositol 3- kinase (PI3K) and subsequently activates protein kinase B (Akt), which downstream signaling conduces to cell survival, inhibition of proliferation and anti-apoptotic effects. Src also activates mitogen-activated protein kinase (MAPK) and its downstream pathway [59]. In contrast, LKB1 and CAMK activation lead to AMPK activation and subsequently to Akt signaling [60]. SR-BI downstream signaling is involved in HDL-induced cyclooxygenase 2 (COX-2) expression and prostacyclin (PGI2) release [61]. Additionally, in endothelial cells has been demonstrated that PI3K downstream signaling, activated by HDL via interaction with SR-BI, promotes the formation of lamellipodia, by Rac-1 activation, inducing cell shape change and proliferation [62,63].

SR-BI activation also controls cholesterol efflux to HDLs. Cholesterol efflux results in inactivation of pathogen-associated molecular patterns (PAMP) signal transduction, and the subsequent activation of NF-kB, reducing chemo- and cytokine expression [37].

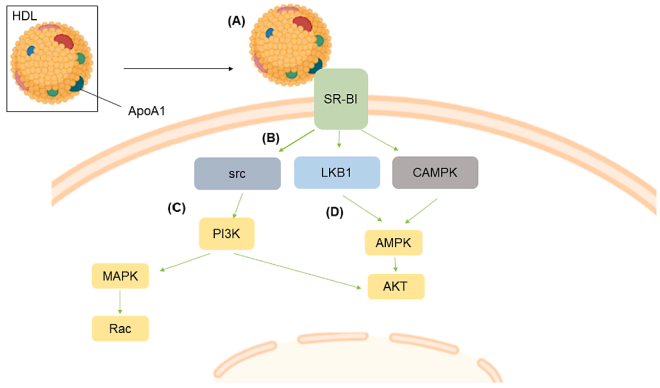

Fig. 1. SR-BI activation derived pathways. (A) SR-BI apoA1 interaction derives in (B) the activation of three different kinases: (C) src that activates PI3K and subsequently MAPK and AKT pathways; (D) LKB1 and CAMPK both activate AMPK and subsequently AKT.
Apoa1, apolipoproteinA1; AMPK, AMP-activated kinase; CAMPK, calcium-calmodulin dependent protein kinase; HDL, high-density lipoprotein; LKB1, liver kinase B1; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; SR-BI, scavenger receptor type B class 1.

3.2. ATP binding cassette transporters

Two types of ATP binding cassette (ABC) transporters can interact with HDLs: ABCA1 and ABCG1. ABCA1 is a transmembrane protein expressed ubiquitously, which interacts with apoA1. ABCA1 function is to transfer phospholipids, mainly transporting phosphatidylcholine over phosphatidylserine to apolipoproteins to form nascent HDLs [64]. ABCG1 is mostly expressed in intracellular membranes where it catalyzes the efflux of phospholipids such as sphingomyelin, cholesterol and its oxygenated derivatives, like hydroxycholesterols [64,65]. ABCA1 and ABCG1 act in combination: ABCA1 recognizes HDLs in the plasma membrane and catalyzes cholesterol efflux from the cell, and ABCG1 allows cholesterol transport to the plasma membrane through the intramembrane system [65].

The ABCA1-apoA1 (Fig. 2) interaction induces the activation of phospholipases C and D and adenylate cyclase through the activation of a trimeric G protein kinase, and the consequent activation of PKC and protein kinase A (PKA), respectively [66,67]. PKC and PKA phosphorylate different substrates and both kinases can alter transcription. PKC activates actin organization pathways, essential for immune synapsis [36,68]. Additionally, upon ApoA1-ABCA1 interaction, cholesterol efflux occurs and phosphatidylcholine and sphingomyelin are also removed from the cell. The decrease in sphingomyelin in the plasma membrane then triggers phosphatidylcholine phospholipase activity, which catalyzes the hydrolysis of phosphatidylcholine to generate diacylglycerol (DAG), a signaling molecule, involved in the activation of PKC and downstream signaling [67]. ABCA1 interacts with Janus kinase-2 (JAK-2), which subsequently activates signal transducer and activator of transcription 3 (STAT3), a protein that inhibits inflammation. Calcium influx is also stimulated by apoA1-ABCA1 interaction, leading to JAK2 phosphorylation [69,70] [59,60]. ABCA1 can couple to cdc42, a GTPase from the Rho family, which directly activates actin polymerization, produces cytoskeleton reorganization and activates kinase cascades [71,72].

ABCA1 and ABCG1 deficiency is related to higher pro-inflammatory cytokine expression and secretion in macrophages, in addition to increased apoptotic responses [73]. Oxidative damage over macrophages is higher when they were depleted from ABCA1 and ABCG1 [74].

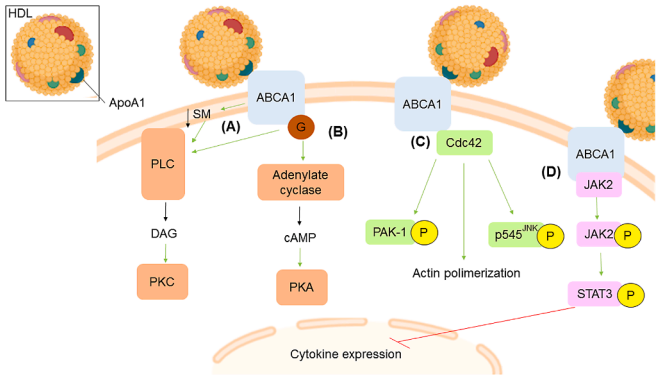

Fig. 2. ABCA1 activation derived pathways. (A) ABCA1 coupled Gα subunit protein activates adenylate cyclase, increasing cAMP concentration and producing PKA activation; (B) the G protein βγ subunits activate PLC, which produces DAG and activates PKC. Additionally, ABCA1 reduces SM content, which activates PLC. (C) ABCA1 activates cdc42, Rho kinase that induces actin polymerization and activates PAK-1 and $p545^{JNK}$ kinases and their subsequent signaling. (D) ABCA1-derived activation of JAK2-STAT3 pathway and cytokine expression depletion.
ApoA1, apolipoprotein A1; ABCA1, ATP binding cassette A1; DAG, diacylglycerol; HDL, high-density lipoprotein; PLC, phospholipase C; PKA, protein kinase A; PKC, protein kinase C; STAT3, signal transducer and activator of transcription 3; SM, sphingomyelin; JAK-2, Janus kinase 2.

3.3. S1P receptors

S1P receptors (S1PRs) are G-protein coupled receptors for S1P. S1PR1 is the most widely studied S1P receptor (Fig. 3). Coupled to a G(i) protein, S1PR1-S1P interaction leads to the activation of pathways such as Ras/ERK, PI3K/Akt, PI3K/Ras and calcium-dependent pathways, as PLC activation is induced [75]. S1PR1-HDL signaling seems to be coupled to apoA1-SR-BI interaction. SR-BI repairs HDLs and enables S1PR1-S1P interaction [76]. The activation of S1PR leads to a signaling cascade that concludes with anti-inflammatory, anti-apoptotic, vasodilation and enhancement of the endothelial barrier [75].

4. HDL and lymphocyte activation

HDLs remove cholesterol from peripheral cells via their interaction with HDL receptors, like ABCA1, ABCG1 and SR-BI. Cholesterol is an essential lipid in lipid rafts, and cholesterol removal can modulate protein attachment to lipid rafts, modulating their functionality. B-cell (BCR) and T-cell receptors (TCR) are localized in lipid rafts and are essential for immune synapsis [77,78], though HDL-immune cell interaction can modulate immune cell activation. Lipid rafts are also essential for antigen presentation because antigen-presenting cells (APCs) express antigen receptors and histocompatibility molecules (MHC) on lipid rafts. Thus, cholesterol efflux from APCs can determine lymphocyte activation [79]. In this sense, macrophages and dendritic cells (DCs) are professional APCs that provide a crucial link between innate and adaptive immunity. Moreover, DCs are key in initiating T-cell responses and determining the adaptive immune response. Briefly, DCs uptake PAMPs, generate MHC-peptide complexes, migrate from the sites of antigen acquisition to secondary lymphoid organs, and finally—as matured DCs—prime naïve T-lymphocytes, thereby driving the adaptive immune response (Fig. 4).

Macrophages and DCs express essential costimulatory molecules, or stimulation of the adaptive cellular response, in the activation process. However, it has been observed that the shifting composition of lipid rafts notably decreases in the presence of cholesterol, downregulating some cellular functions. Notably, HDL or apoA1 are involved in interaction with ABCA1 or ABCG1, removing cholesterol from the lipid rafts in macrophages and DCs [80,81]. Thus, HDL negatively regulates T-cell activation and the expression of inflammatory mediators in professional APCs. In macrophages, T-cell inactivation is caused by decreased macrophage expression of MHC class II, a lipid raft component critical to antigen presentation [78,82,83]. ApoA1 inhibits the differentiation of monocytes to DCs by increasing monocyte secretion of prostaglandin E2 (PGE2) and IL-10 [84]. It also inhibits T-lymphocyte activation by decreasing antigen presentation in differentiated DCs [85]. In contrast, immune cells express HDL receptors on their plasma membranes, and HDL-induced pathways are activated through interaction with HDL receptors.

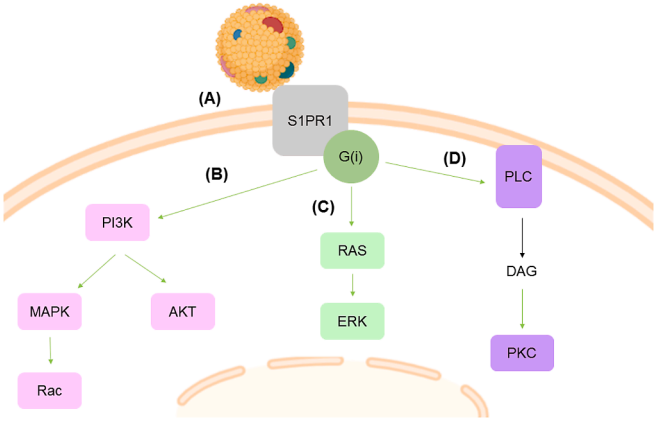

Fig. 3. S1PR1 activation derived pathways. (A) HDLs interact with S1PR1, receptor coupled to a G(i) protein, which activates: (B) PI3K signaling and the subsequent MAPK and AKT pathways; (C) RAS pathway and (D) PLC that activates PKC.
ERK, extracellular-signal-regulated kinase; PI3K, phosphatidylinositol 3-kinase; MAPK, mitogen-activated protein kinase; AKT, protein kinase B; PKC, protein kinase C; S1P1R1, sphingosine-1-phosphate receptor 1.

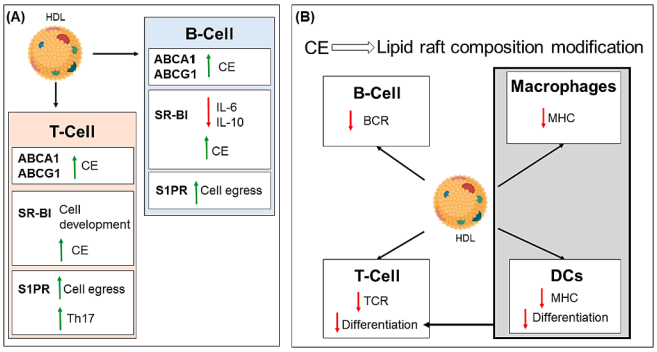

Fig. 4. HDL and lymphocyte activation. (A) HDL interaction with lymphocyte receptors: In T-cells ABCA1 and ABCG1 activation stimulates CE from the cell; SR-BI activation stimulates CE and is essential for T-cell development; additionally, S1PR stimulates T-cell egress from the thymus and T-cell differentiation into Th17 phenotype. In B-cells, ABCA1 and ABCGA1 and SR-BI activation stimulates CE; SR-BI activation reduces IL-6 and IL-10 production and S1PR activation is essential for B-cell egress from the bone marrow. (B) CE efflux effects over immune system cells: Cholesterol efflux reduce cholesterol content of lipid rafts, lipid raft compositional modifications reduce BCR and TCR localization in the cell membrane, reducing B- and T-cell activation, respectively. Lipid raft cholesterol reduction lower monocyte differentiation into DCs and in mature DCs and macrophages reduces MHC localized in the cell membrane, reducing antigen presentation. HDL, high-density lipoprotein; ABCA1, ATP-binding cassette A1; ABCG1, ATP-binding cassette G1; CE, cholesterol efflux; SR-BI, scavenger receptor type B class 1; S1PR, sphingomyelin 1 P receptor; IL, interleukin; BCR, B-cell receptor; TCR, T-cell receptor; DCs, dendritic cell; MHC, major histocompatibility complex.

4.1. HDLs and B-cells

Lipid rafts on B-cells are essential for BCR signaling. After antigen recognition, BCR moves to lipid rafts and the BCR-antigen complex is internalized for activation of T-cells. Lipid raft modulations alter BCR activation and antigen presentation to T-cells. When B-cells interact with HDLs, cholesterol is removed from lipid rafts, and the anchoring of BCR in lipid rafts becomes less effective [85].

SR-BI activation in B-cells downregulates IL-6 and IL-10 cytokine expression. Other SR-BI derived pathways can be activated, influencing B-cell proliferation and survival. SR-BI null mice exhibited impaired B-cell homeostasis and higher lymphocyte numbers [86].

B-cells also express a variety of S1PRs, and S1P exerts different functions over B-cells. For example, S1P signaling is essential for B-cell egress from the bone marrow [87,88]. In addition, S1P signaling regulates the migration of follicular and peritoneal B-cells [88,89].

4.2. HDLs and T-cells

TCRs are localized in lipid rafts and HDL T-cell interaction can modulate TCR activation and T-cell functions [77,78]. In addition, cholesterol efflux from APCs, as described above, can reduce antigen presentation and, consequently, T-cell activation [78,90]. T-cells express SR-BI, ABCA1 and ABCG1, and HDLs are recognized through these receptors leading to cholesterol efflux [91]. SR-BI has been described as essential to lymphocyte homeostasis. SR-BI inhibition provokes impaired T-cell development and delayed thymus regeneration [92].

Additionally, lymphocytes express different S1PRs responsible for

diverse actions. S1P signaling over lymphocytes regulates lymphocyte egression from the thymus, specifically through S1PR1 signaling [93]. In addition, S1P signaling reduces Th17 cell differentiation by S1PR1 [94].

5. Conclusions

A strong relationship between HDLs and cardiovascular or metabolic diseases has been extensively reported in the literature. HDL functions as an anti-inflammatory and antioxidant agent, as well as HDL role facilitating reverse cholesterol transport, relate to the onset and progression of atherosclerosis or other metabolic diseases associated with oxidative stress, including inflammatory diseases. It has also been established that lipoprotein homeostasis does not rely on the amount of HDL circulating, but on the molecular composition and functionality of HDL. Both parameters differ under physiological and pathological conditions. Progressive inflammation that occurs during chronical diseases influence HDL population and enzymatic activity of lipids and proteins, as well as the interaction of HDL with membrane receptors responsible of intracellular signaling cascades. Regarding our immune cell populations, removal of excess cellular cholesterol from lipid rafts by HDLs influence antigen-presentation activity prior to lymphocyte activation. Our study highlights the importance of high-density lipoproteins for an appropriate control of whole-body lipoprotein metabolism, preventing an imbalance that may lead to cellular cholesterol accumulation, as well as the key role of HDLs in the various interactions with membrane immune cell receptors during inflammation or innate and adaptive immunity events. Further studies are needed to elucidate the remodeling of HDL in order to design prevention strategies and therapies for cardiovascular and metabolic current diseases.

Abbreviations

ABC	ATP binding cassette
Akt	Protein kinase B
APC	Antigen presenting cell
apo	Apolipoprotein
ATF3	Activating transcription factor 3
BCR	B-cell receptor
CAD	Coronary artery disease
CAMPK	Calcium-calmodulin dependent protein kinase
CEC	Cholesterol efflux capacity
COX	Cyclooxygenase
CVD	Cardiovascular disease
DC	Dendritic cell
GSH	Glutation peroxidase
HDL-C	High-density lipoprotein-cholesterol
HII	HDL inflammatory index
IL	interleukin
JAK2	Janus kinase 2
LCAT	Lecithin cholesterol acyl transferase
LPS	Lipopolysaccharide
LpPLA2	Lipoprotein-associated phospholipase 2
LKB	Liver kinase B
MAPK	MAP kinase
MHC	Major histocompatibility complex
NF-kB	Nuclear factor kappa-light chain enhancer of activated B-cell
ox-LDL	oxidized low-density lipoprotein
PAMP	Pathogen-associated molecular pattern
PGI2	Prostacyclin 2
PGE2	Prostaglandin E2
PI3K	Phosphatidylinositol 3-kinase
PKA	Protein kinase A
PKC	Protein kinase C
PLC	Phospholipase C
PON1	Paraoxonase 1
p-IKK	Phosphorylated IKB kinase
RCT	Reverse cholesterol transport
SAA1	Serum amyloid A1
SR-BI	Scavenger receptor class B type 1
STAT3	Signal transducer and activator of transcription 3
S1P	Sphingomyelin 1 phosphate
S1PR	S1P receptor
TCR	T-cell receptor
TLR	Toll-like receptor

Declaration of competing interest

The authors state no conflict of interest.

Data availability

No data was used for the research described in the article.

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