High-Density Lipoproteins as Bidirectional Lipid Vectors

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The anti-atherogenic properties of high-density lipoproteins (HDL) have been explained mainly by reverse cholesterol transport (RCT) from peripheral tissues to the liver. The RCT seems to agree with most of the negative epidemiological correlations between HDL cholesterol levels and coronary artery disease. However, therapies designed to increase HDL cholesterol failed to reduce cardiovascular risk, despite their capacity to improve cholesterol efflux, the first stage of RCT. Therefore, the cardioprotective role of HDL may not be explained by RCT, and it is time for new paradigms about the physiological function of these lipoproteins. It should be considered that the main HDL apolipoprotein, apo AI, has been highly conserved throughout evolution. Consequently, these lipoproteins play an essential physiological role beyond their capacity to protect against atherosclerosis.

high-density lipoproteins Lipid Insulin

1. Introduction

High-density lipoproteins (HDL) are complex macromolecules consisting of amphipathic lipids on the surface (free cholesterol and phospholipids) and non-polar lipids in the core (cholesteryl esters and triglycerides) [1][2]. The complex is stabilized by proteins named apolipoproteins, such as apolipoprotein (apo) AI, apo AII, apo AIV, the apo Cs, apo D, apo E, apo M and apo J [1]; apo AI and apo AII are the most abundant proteins, with the former representing up to 70% of the HDL protein mass [1][2].

The inverse relationship between the concentration of HDL cholesterol (HDL-C) and the risk of coronary artery disease is well known [1][3] and presupposes a causal relationship. For many years, HDL have been considered anti-atherogenic particles due to their ability to promote cholesterol efflux and their anti-oxidant, anti-aggregating, anti-coagulant, and anti-inflammatory properties [1][2]. The main anti-atherosclerotic mechanism associated with HDL is the reverse cholesterol transport (RCT), in which cholesterol from peripheral tissues is picked up by HDL and ultimately returned to the liver for its excretion or recycling [1][2][3].

RCT seems in agreement with most of the epidemiological observations regarding the relationship between cardiovascular risk and plasma levels of HDL-C. Early interpretations considered HDL-C plasma concentrations as a marker of the number of HDL particles and the amount of cholesterol efflux from tissues [3]. Today, the concept of HDL functionality, particularly its capacity to promote cholesterol efflux (the first step of RCT), has replaced HDL-C as a biomarker of coronary artery disease (CAD) risk [4]. In addition, there are some reports of CAD patients with high levels of HDL-C but with poor levels of phospholipids, which results in a decreased cholesterol efflux capacity

(CEC) [5], suggesting that the quality of HDL is also a determinant of HDL function. Although CEC may predict CAD [6], this in vitro test does not seem to be independent of HDL-C levels in untreated CAD patients and in well-matched controls [6] or of inflammation markers such as high-sensitivity C-reactive protein [7]. It is also unknown whether CEC is, in fact, a good biomarker of the whole RCT.

Importantly, therapies designed to raise HDL-C, despite increasing HDL-induced CEC [6][8], failed to reduce cardiovascular risk. In addition, studies of mutations in genes related to the metabolism or structure of HDL revealed that very low HDL levels do not necessarily lead to increased cardiovascular risk [1][3]. These observations indicate that RCT may not explain the cardioprotective role of HDL. Other properties of HDL have been suggested as responsible for their anti-atherogenic potential [1]. It is obvious that the role of these lipoproteins is essential for life because HDL has been conserved throughout evolution, from cartilaginous fish to humans [9]. For the same reason, it is also apparent that their original biological role may not be to protect arteries against atherosclerosis via the RCT. Therefore, based on the actual evidence, it is time to reconsider the physiological function of HDL and establish new paradigms that must also explain the overall beneficial properties of these lipoproteins.

2. HDL as Lipid Vectors

The main site of cholesterol synthesis is the liver, which produces about 50% of the total cholesterol in the body [10]. Then, cholesterol should reach the peripheral tissues packed in a lipoprotein, i.e., very-low-density lipoproteins (VLDL). The intravascular lipolysis of triglycerides contained in VLDL leads to LDL formation, which are the lipoproteins with the largest content of cholesterol in humans. Consequently, they have been considered the major cholesterol vehicle to the tissues [11]. However, there are important issues that do not support this hypothesis: (1) the main function of VLDL is the transport of triglycerides from the liver to the tissues, and these particles become enriched with cholesterol intravascularly; (2) the majority of the cholesterol from VLDL/LDL is returned to the liver; and (3) some tissues lack detectable uptake of cholesterol mediated by LDL-receptors [12]. This suggests when a cell's cholesterol needs to increase, i.e., tissue repair, replication or growth, the quantity of cholesterol that it could receive from LDL would not be enough. Instead, the bi-directional HDL transporter SR-BI is widely expressed in most organism cells [13]. Moreover, besides VLDL, HDL is the other class of lipoproteins synthesized by the liver, suggesting that these lipoproteins may carry the hepatic cholesterol to extrahepatic tissues.

Results from laboratory and other research groups support the hypothesis that HDL delivers lipids, probably from the hepatic origin, to cells [14]. HDL delivers cholesterol and sphingomyelin to endothelial cells in culture [14]. Importantly, the kinetics of internalization of the former is faster than that of the latter; most of the cholesterol from HDL is integrated into the cells within the first 30 min of incubation in an SR-BI-independent manner. This cholesterol pathway may implicate other HDL receptors, such as the F(1)-ATPase/P2Y(13) complex [15][16]. In contrast, sphingomyelin is delivered after 30 min of incubation following the same internalization kinetics as apo AI [14]. These data suggest that cholesterol dissociates from HDL to be delivered to the cell, and the remaining particle is further internalized. The endothelial cells internalize cholesterol from HDL despite very high concentrations of LDL cholesterol [14]. These results suggest that the extrahepatic cells can take up cholesterol from HDL rather than

from LDL (which requires the presence of ApoB receptors). They are consistent with earlier studies demonstrating that HDL inhibited LDL uptake by bovine endothelial cells [11][17][18].

Besides cholesterol, HDL delivers sphingomyelin to endothelial cells in culture, which mediates eNOS activation via phosphorylation and ICAM-1 expression [14]. These results suggest that some of the beneficial effects of HDL on vascular functions depend upon sphingomyelin. Taking into account the high complexity of HDL, which includes over 200 species of lipids and about 85 different proteins [19][20][21][22], the universe of possible effects of these lipoproteins on cell function after the internalization and delivery of their content is extremely high. The wide effects that have been attributed to HDL in health as well as in disease are more comprehensible [22][23].

Focusing only on lipid delivery, the contribution of HDL becomes of particular importance when cell membranes should be intensively synthesized or re-structured, i.e., during fetal development, tissue repair, intensive intracellular vesicle fusion with a plasmatic membrane, and cancer processes, as mentioned below.

2.1. The Role of HDL in Tissue Repair during Acute Phase Response and Inflammatory Processes

Besides the anti-inflammatory role of HDL from intestinal origin mentioned above [24], HDL-C plasma levels and composition may change drastically during inflammatory processes. A significant HDL-cholesterol level decrease is observed during sepsis [25], diffuse axonal injury [26], neural injury [27], and acute coronary syndrome [28], among others. In the same line of evidence, HDL protects against doxorubicin-induced cardiotoxicity in mice [29], whereas increased plasma levels of HDL induced by the CETP inhibitor des-fluoro-anacetrapib inhibits intimal hyperplasia in New Zealand White rabbits subjected to endothelial denudation of the abdominal aorta [30]; importantly, both effects were dependent of SR-BI.

The dramatic modifications of HDL structure during inflammation or tissue injury [31][32][33][34][35] strongly suggest a short-term rescue mechanism for cell survival when facing the insult. Besides the capacity of HDL to scavenge lipopolysaccharides produced during damage to the tissues driven by infectious processes [36][37], HDL seems to participate as carriers of lipids from dead cells after acute tissue injury [38][39]. Such lipids need to be recovered and reintegrated into the still viable cells and new cells for tissue repair. This role of HDL may be enhanced by amyloid A (AA) peptides [38]; during tissue injury, mediators of inflammation, i.e., IL-1β, and TNFα, induce the expression of serum AA, which becomes associated mainly with HDL [31]. The physiological role of amyloid A has not been completely understood but seems to lead HDL to the site of the injury [39][40]. It can also be speculated that AA fulfills the role of a transient apolipoprotein [41] intended to increase the capacity of HDL to deliver lipids to the cells via SR-BI [42]. SR-BI is one of the putative receptors for AA that induces HDL internalization [42]; congruently, HDL isolated from *Scarb1*-deficient mice (*SR-BI*$^{-/-}$) are enriched in AA [43]. As described above, some of the HDL functions are mediated by their sphingomyelin content, and in turn, sphingomyelin is internalized to endothelial cells via SR-BI [14]. Then, AA may enhance the capacity of HDL to deliver functional and structural lipids to cells during the acute phase. In addition, the AA displaces some apolipoproteins [31][44], including apo AI [38], from HDL. The displaced apolipoproteins provide the opportunity of integrating supplementary HDL particles to manage the

necessity of lipid transport and delivery during the acute phase. Importantly, the AA is a highly conserved protein along with evolution, similar to apo AI [9][38][40][45], suggesting a long-term adaptative interaction between both proteins.

The proposed role of HDL as a critical lipid vector for tissue repair after an injury is in agreement with several observations; as described above, patients with an acute coronary syndrome whose HDL-C plasma levels drop below 30 mg/dL had an odds ratio = 2.0 of intrahospital death [28]. Viable cells after the coronary event require rescue and repair, increasing the need for lipids for membrane restoration. The availability of such lipids in HDL helps promote the more efficient and faster recovery of damaged cells and, consequently, increases the possibility of survival. In the absence of enough lipid vectors, tissue repair would not be as fast as required to warrant the recovery of the organ function. The correct restoration of the endothelium in rabbits with increased HDL levels previously described [30] also supports this idea further. Whether the increase in HDL during the acute phase provides additional protection and helps repair tissues other than the cardiovascular system as suggested by previous reports [26][27][29][46] warrants future research.

2.2. HDL in Fetal Development

Embryogenesis and fetal development require large amounts of cholesterol and other lipids for normal development. The cholesterol of de novo synthesis in fetal cells is the main source of this lipid in the fetus [47]. The second source of fetal cholesterol is the mother; this exogenous cholesterol is transferred from the mother's HDL to the syncytiotrophoblast of the placenta. Cholesterol is acquired from the maternal plasma HDL through the apical side of the syncytiotrophoblast layer, which expresses SR-BI [48]. This observation is consistent with the early described role of SR-BI in the internalization of cholesterol from HDL [49]. Then, the acquired cholesterol reaches the villous stroma and is transported by the endothelium of the fetal circulation. Accordingly, the fetuses of mice dams not expressing apo AI (Apoa1$^{-/-}$) were 25% smaller than controls and had less cholesterol mass by fetus [50]. Importantly, the endogenous production of cholesterol by the fetus from Apoa1$^{-/-}$ dams was comparable to that of controls, emphasizing the contribution of maternal HDL as cholesterol vectors to fetal development [50]. In the same context, Santander et al. [51] demonstrated that embryos lacking SR-BI exhibit a high prevalence of neural malformations and contain less cholesterol than normal littermates. Importantly, female mice deficient in SR-BI are infertile, probably due to abnormalities in the viability and developmental potential of their oocytes [52]. In addition, SR-BI-deficient pups exhibited intrauterine growth restrictions. The SR-BI is involved in the maternal-fetal transport of cholesterol and/or other lipids with a role during neural tube closure and fetal growth [51].

Once the lipids from the mother or synthesized by the fetus reach the fetal circulation, they are transported and delivered mainly by HDL; during these stages of intense cell proliferation, more than 50% of the cholesterol and other lipids are contained in HDL [47][53][54]. Fetal HDL are larger than in adults, and they are particularly rich in apo E[47]. As expected, the intravascular metabolism of HDL in fetal circulation differs from that of adults; previous studies demonstrated that the activity of CETP is significantly lower in umbilical cord than in the mothers [51][52][53][54]. Taken together, the low CETP activities, the large HDL observed in fetal circulation, and the high impact of SR-

BI receptor on embryo development [51], it is plausible to conclude that HDL functions as vectors of lipids for tissues during intrauterine development.

2.3. HDL in Cancer

Malignant cell survival requires large amounts of nutrients and lipids for membrane structure; consequently, cholesterol supply is needed for tumor development. The contribution of HDL to the growth of malignant cells is controversial and seems to depend on the type and localization of the tumor. Particularly, HDL can stimulate the growth of both estrogen-dependent and independent breast cancer cells in vitro [55]. Additionally, HDL induced the proliferation of androgen-independent prostate cancer cells [56]. These findings are consistent with an increased SR-BI expression in Leydig cell tumors, nasopharyngeal carcinoma, prostate cancers, and some breast cell lines such as HBL-100 and MCF-7 [57][58][59]. The role of SR-BI has been described mainly in breast and prostate cancers; for these tumors, the internalization of cholesterol from HDL via SR-BI enhances the tumor progression and aggressiveness [55][60]. Accordingly, with the preference for cholesterol from HDL in HMEC-1 cells [14], metastatic prostate tumors overexpress SR-BI receptors but not LDL receptors [60]. Consistently, down-regulation of SR-BI in prostate cell lines resulted in decreased cellular viability [61] and inhibition of motility of nasopharyngeal cancer cell lines [62]. These observations support the idea that one of the main physiological roles of HDL is to be carriers of lipids for cells in development. Since the mechanism of lipid delivery to the cells by HDL involves the internalization of the lipoprotein particle [14][63][64], it is reasonable to postulate cancer treatments with reconstituted HDL, including antitumoral molecules in their structure [57][65].

3. HDL Contribution to Insulin Secretion

The efflux of lipids is also a proven property of HDL that may play an important role in insulin secretion besides the importance of lipid influx promoted by HDL. Low plasma levels of HDL in type 2 diabetes mellitus have been considered a consequence more than a contributor to pancreatic β-cell dysfunction; increased triglyceride transfer from VLDL in coordination with hepatic lipase activity [2][66] and a high clearance rate of methylglyoxal-modified apo AI [67] have been accepted as some of the main causes of hypoalphalipoproteinemia in this physiopathological condition. However, there is increasing evidence for an important role of HDL in glucose homeostasis and insulin secretion by pancreatic β-cells [68][69][70]. Accordingly, a pharmacological increase of HDL with CETP inhibitors was associated with a significant rise in insulin plasma concentration [69] and with a significant risk reduction of new onset of diabetes in patients treated with dalcetrapib [71]. Since HDL has been demonstrated to promote cholesterol efflux from β-cells in culture [69][70][72], it has been argued that HDL prevents lipotoxicity induced by oxidized LDL and accumulation of cholesterol in β-cells [70][72]. However, there is no plausive evidence that demonstrates a cholesterol accumulation reaching toxic levels in β-cells in vivo.

It has been shown that about 9000 [73] insulin granules are contained in each β-cell, which is equivalent to more than 30 times the cell surface area. Every time plasma glucose concentrations increase, a large number of granules fuse with the cytoplasmatic membrane for insulin exocytosis. As a result, there is a constant cell surface expansion that should be compensated by continuous cytoplasmic membrane endocytosis [74][75]. In fact, when

such endocytosis is impaired, the β-cell dysfunction is unable to secrete insulin in response to increased glucose concentrations, leading to glucose intolerance, as demonstrated in mice [75]. Thus, HDL may contribute to regulating and finely adjusting β-cell plasma membrane lipid composition [70] and insulin secretion by delivering sphingolipids [14][76][77].

It has been demonstrated that sphingomyelin-derived lipids, particularly sphingosine and sphingosine-1-phosphate, modulate the docking, Ca^{2+} sensitivity, and membrane fusion during exocytosis of granule contents [76][77]. As stated before, sphingomyelin may be delivered to cells by HDL [14], thus raising the possibility of contributing these lipoproteins to the β-cell function by maintaining its sphingomyelin supply. This explanation is consistent with recent reports that demonstrated an enhanced insulin secretion when MIN-6 β-cells were incubated with HDL [70]. The same study [70] demonstrated an increased cholesterol efflux promoted by HDL, as observed in several previous works with different types of cultured cells. It is important to emphasize that HDL promotes not only cholesterol but also phospholipid efflux from cultured cells [78][79]; in other words, HDL recovers membrane fragments from cells. Therefore, it is likely that HDL removes excess membrane lipids, i.e., from granule-mediated secretory cells, even if studies have been biased exclusively toward cholesterol efflux. Therefore, in addition to membrane endocytosis, HDL may contribute to compensate for the excess membrane lipids derived from vesicle fusion (exocytosis). Consistently with this idea, patients with Tangier disease are characterized by an impaired HDL-mediated lipid efflux [80][81] and concomitant glucose intolerance and decreased insulin secretion [82]. In the same vein, the ABC-A1 polymorphism rs9282541 that results in a substitution of arginine 230 for cysteine is associated with the increased incidence of type 2 diabetes mediated by HDL cholesterol plasma levels [83]. Finally, a recent meta-analysis demonstrated that CETP inhibitors decrease the risk of new-onset of diabetes by 16%, concomitantly with significant increases in HDL-C [84].

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