Clinica Chimica Acta 415 (2013) 94–100

Contents lists available at SciVerse ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Invited critical review

HDL drug carriers for targeted therapy

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ARTICLE INFO

Article history:
Received 12 August 2012
Received in revised form 6 October 2012
Accepted 7 October 2012
Available online 12 October 2012

Keywords:
HDL
Caveolae
SR-BI
LCAT
MicroRNAs
Targeted therapy

ABSTRACT

Plasma concentrations of high-density lipoprotein cholesterol (HDL-C) are strongly and inversely associated with cardiovascular risk. HDL is not a simple lipid transporter, but possesses multiple anti-atherosclerosis activities because it contains special proteins, signaling lipid, and microRNAs. Natural or recombinant HDLs have emerged as potential carriers for delivering a drug to a specified target. However, HDL function also depends on enzymes that alter its structure and composition, as well as cellular receptors and membrane microdomains that facilitate interactions with the microenvironment. In this review, four mechanisms predicted to enhance functions or targeted therapy of HDL in vivo are discussed. The first involves caveolae-mediated recruitment of HDL signal to bind their receptors. The second involves scavenger receptor class B type I (SR-BI) mediating anchoring and fluidity for signal-lipid of HDL. The third involves lecithin-cholesterol acyltransferase (LCAT) concentrating the signaling lipid at the surface of the HDL particle. The fourth involves microRNAs (miRNAs) being delivered in the blood to special targets by HDL. Exploitation of these four mechanisms will promote HDL to carry targeted drugs and increase HDL's clinical value.

Contents

1. Introduction

Epidemiology has demonstrated an inverse relationship between high-density lipoprotein (HDL) levels and cardiovascular disease (CVD) risk [1]. Each HDL particle contains hundreds of proteins and lipids, which endow HDL with several functions. However, recent studies have suggested that total HDL is not the best marker for measuring CVD risk [2]. It has been assumed that the varied physiological functions of HDL are a result of heterogeneity among the components of HDLs. Moreover, not only the quantity but also the quality of HDL is an important feature of its atheroprotective function. It is worth noting that enzymes, which alter HDL structure and component composition, as well as cellular receptors and membrane micro-domains play significant roles in regulating HDL function. For example, the caveolae contain many HDL receptors and their membrane micro-domains amplify signaling cascades for HDL [3]. Whether the structure of caveolae promotes HDL signaling function remains unclear. Second, some enzymes can promote the maturation of HDL and lipid transporting [4], but whether or not these enzymes can enhance HDL signaling effect remains unknown. Third, many components of HDL have cognate receptors expressed on various or specific cell types. Whether there is reciprocity among such

Abbreviations: HDL, high-density lipoprotein; SR-BI, scavenger receptor class B type I; eNOS, endothelial nitric oxide synthase; miRNAs, microRNAs; S1PRs, sphingosine 1-phosphate receptors; S1P, sphingosine 1-phosphate; PGI2, prostaglandin I2; COX-2, cyclooxygenase-2; FC, free cholesterol; LCAT, lecithin-cholesterol acyltransferase; BD, Behçet's disease; ApoA-I, apolipoprotein A-I; siRNA, small interfering RNA; Toc-siRNA, alpha-tocopherol-conjugated siRNA; BBB, blood–brain barrier; FH, familial hypercholesterolemia disorder; nSMase2, sphingomyelinase; FTY720, Fingolimod; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

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http://dx.doi.org/10.1016/j.cca.2012.10.008

receptors remains unknown, but some studies have suggested that scavenger receptor class B type I (SR-BI) can promote other receptors' efficacy for HDL. Finally, microRNAs (miRNAs) have been shown to exert therapeutic effects in the human body, and HDL may be developed as a carrier to deliver special miRNAs [5]. Thus, does dysfunction of some enzymes, micro-domains, or HDL component-related receptors underlie HDL disorders? In this review, we predict four molecular mechanisms that may be exploited to enhance the signal and functions of HDL and speculate on how we can manipulate these potential mechanisms to prevent and counteract diseases in clinic.

2. Caveolae recruit HDL signals to bind their receptors

Caveolae are special plasma membrane invaginations in many vertebrate cell types, which are especially prevalent in endothelial cells and adipocytes. Caveolin oligomers associate with cholesterol and sphingolipids in certain areas of the cell membrane, leading to the formation of caveolae. Biochemical studies have revealed that caveolae are detergent resistant, highly hydrophobic cell membrane domains [6]. Caveolae, as type of lipid raft, compartmentalize signal transduction molecules, which regulate myriad cellular functions. They are also an important locale of lipid transport, due to the high concentration of enzymes and HDL receptors [7]. Nevertheless, there is a dispute whether caveolae are stable invaginated raft subdomains [8] or merely a reflection of the process of endocytosis [9]. Even so, caveolae provide a platform for signal transduction and lipid traffic, facilitating either transient or permanent effects. Here, we will discuss the potential of caveolae structure to promote HDL action.

Caveolae are 50–100 nm invaginations in the plasma membrane. They represent a locale wherein HDL and its receptors may come into contact and be moderately sheltered from the high-flow speed in the lumen of the blood vessel (Fig. 1A). Studies have demonstrated that flow-preconditioned cells express a 5-fold increase in caveolin at the luminal surface, as compared to no-flow controls. The density of caveolae was also shown to be enhanced 6-fold at the luminal cell surface of flow-conditioned cells [10]. Functionally, sterol exchange between caveolae and lipoproteins is faster than on non-raft domains [11], and it was theorized that lipoproteins have plenty of time to exchange lipids in caveolae domains. Upon stimulation (e.g., HDL), caveolin-1 and caveolae may allow for the proper organization of various signal transduction pathways, such as endothelial nitric oxide synthase (eNOS) activation [12,13]. Furthermore, caveolin-1 knock-out carotids showed reduced flow-dependent signaling and coupling of eNOS activity [14,15]. To illustrate HDL stimulation of eNOS in caveolae of endothelial cells, eNOS activation was measured in caveolae membranes not noncaveolae membranes [16]. These results indicated caveolae are the regulatory mechanism under blood flow circumstances for resorting large-sized signaling particles (Fig. 1B).

Quantum dots (QD), which have superior photoemission and photo-stability characteristics, are novel tools in biological and medical applications. A QD-based study showed that caveolae/lipid rafts colocalize, but that the lipid rafts are more enriched for QD than the caveolae. It was thus theorized that caveolae may only allow smaller size QD to wrap tightly [17].

The diameter of HDLs ranges from 8 to 13 nm. They can assemble in caveolae domains, which are described as 50–100 nm invaginations. However, other lipoproteins (LDL and VLDL, 18–28 nm and 60–200 nm in diameter, respectively) [18] have few or no such possibilities for accumulation in such cramped space (Fig. 1C). One study reported that SR-BI, which is concentrated in caveolae [19], binds lipoproteins in the following order of affinities: VLDL > HDL > LDL. In contrast, effectiveness in SR-BI-mediated efflux of cholesterol from peripheral cells was shown to occur in the order of HDL > VLDL, LDL [20]. The possible reason for this may be that HDL is easier bound with SR-BI located on caveolae than LDL or VLDL.

3. SR-BI mediates anchoring and fluidity for signal-lipid of HDL

Interestingly, cross-linking studies indicted that HDL does not directly interact with caveolin-1, but does interact with its components' receptors located in caveolae [21]. Consistent with this idea, SR-BI was shown by immunofluorescence to colocalize with caveolin-1 [22]. Moreover, a study reported an important role for cholesterol and SR-BI in the regulation of caveolin function and stabilization [23]. Binding of HDL to SR-BI also facilitates the bidirectional flux between HDL and plasma membrane via reorganization of lipids within caveolae-rich domains [24]. These findings suggest that the interactions between SR-BI and caveolae have a mutually beneficial effect. Apart from that, many receptors have been shown to colocalize with SR-BI in caveolae domains. For example, HDL-associated estradiol stimulates eNOS and vasodilation in a SR-BI-dependent manner [25]. Some studies found that both SR-BI and sphingosine 1-phosphate receptors (S1PRs) were clustered in the caveolae region [26]. Still other evidence has indicated that S1PRs-mediated HDL-sphingosine 1-phosphate (S1P) biological effect was blocked in SR-BI knock-out mice (>65% of the S1P in blood was associated with HDL [27]). This suggested a functional synergy between S1PRs and SR-BI [28,29]. Our lab demonstrated that knockdown of SR-BI significantly reduced prostaglandin I2 (PGI_2) release and cyclooxygenase-2 (COX-2) expression induced by HDL-S1P [30]. In this process, binding of HDL-S1P to S1PR occurs through the anchoring of SR-BI [31]. This anchoring effect contributes to increasing reaction time between HDL-S1P and S1PR, and acts to further overcome the high-flow speed in the lumen of the blood vessel (Fig. 2A).

On the other hand, SR-BI mediates both selective uptake of cholesteryl ester from HDL to cells [32] and bidirectional free cholesterol (FC) movement [33]. It is worth noting that the movement of FC via SR-BI depends on the direction of the FC gradient [34]. Moreover, SR-BI-mediated HDL-S1P transport may require not only the formation of a "productive complex" but also a certain concentration [35]. Like the aqueous diffusion mechanism, lipid exchange induced by SR-BI increases the liquidity of signaling lipids on the surface (HDL and plasma membrane), thereby increasing the bonding opportunity between signaling lipids and their receptors (Fig. 2B). In other words, S1P transport and interaction with its receptors are accomplished simultaneously and localization of this complex is mediated by SR-BI. Thus, there are two mechanisms by which SR-BI may amplify HDL signal cascades: 1) anchoring effect, and 2) raising fluidity for the HDL signal-lipid.

4. Lecithin-cholesterol acyltransferase (LCAT) concentrates the signal lipid at the surface of the HDL particle

Some diseases have been associated with both HDL levels and HDL size [36]. From the smallest pre-beta-1 HDL to the large alpha-1 HDL, the particle size of HDL can gradually vary as it takes on different components [2]. In this increscent process, HDL may accept some substances that have atheroprotective effects. Epidemiological studies have suggested that large-sized HDL has potent antiatherogenic properties [37–39]. In fact, high pre-beta-1 levels have been associated with increased CVD risk [40]. Behçet's disease (BD) is an inflammatory vasculitis, and evidence for accelerated atherosclerosis in BD has been observed. A reduction in the HDL_2 subpopulation and an increase in the HDL_3 subpopulation has been observed in BD patients [41]. This result suggested that HDL_2 have a more robust anti-inflammatory function than HDL_3. Still other data indicated that a high level of HDL_3 is associated with metabolic syndrome [42,43].

The HDL surface contains a wide variety of lipids that participate in cellular signal transmission. As the HDL size increases, these signaling lipids become enriched on the HDL surface. LCAT is an enzyme that converts FC into cholesterylester, which is then sequestered into the core of a lipoprotein particle. It is worth noting that cholesterol is required to maintain membranes and can reduce membrane fluidity. The hydroxyl group on cholesterol interacts with the polar head groups