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HIGH-DENSITY LIPOPROTEIN: ROLE IN REVERSE CHOLESTEROL TRANSPORT

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ABSTRACT: High-density lipoprotein (HDL) mediates reverse cholesterol transport (RCT) through its potential to accept excess cholesterol from extrahepatic tissues, and delivers it to the liver for breakdown and excretion. HDL also has pleiotropic properties such as anti-apoptosis, anti-inflammation, and capacity to remove oxidized sterols and phospholipids from the circulation. HDL is composed of apolipoprotein A-I, the major lipoprotein and apolipoprotein A-II, the minor lipoprotein. For HDL to carry out reverse cholesterol transport, it has to transform to make it suitable for acceptance of cholesterol and phospholipids. Therefore, in this review, we explore the composition and the various sizes of HDL. Further, we review the biosynthesis and remodeling of HDL by various proteins, enzymes and receptors such as ATP-binding cassette transporter class B-1 (ABCA1), endothelial lipase (EL), scavenger receptor class B type I (SR-BI), cholesteryl ester transfer protein (CETP), lecithin cholesterol acyltransferase LCAT), and phospholipids transfer protein (PLTP). Finally, we describe the pathways involved in the removal of cholesterol from the peripheral tissue and the current therapeutic strategies to increase levels of HDL-C as well as their outcomes.

INTRODUCTION: Reverse cholesterol transport (RCT) is a concept that was described by John Glomset as the removal of cholesterol from peripheral tissues back to the liver. In his work, he noticed that excess cholesterol from the peripheral tissues was delivered to the liver for excretion, which was attributed to protection conferred against cardiovascular disease [1-4]. This idea concurs with studies that have linked low levels of HDL to increased incidence of cardiovascular disease [5, 6]. Therefore, this review provides an insight into how high-density lipoprotein (HDL) undergoes different structural transformations while transporting cholesterol and triglycerides.

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This review also highlights the various factors that are involved in remodeling HDL, as well as the different pathways that are involved in cholesterol efflux, which in turn may encourage research into how high-density lipoprotein could be used in future therapies.

High - Density Lipoprotein: High - density lipoproteins are a group of lipoproteins composed of lipids and lipoproteins with sizes ranging from 7.5 nm to 15 nm. HDLs can be classified into different categories based on their electrophoretic mobility, density, particle size, and apolipoprotein composition [8], and may assume spherical or discoidal shapes [9]. The concentrations of lipid and apolipoprotein contents in HDL particles differ, thus, enabling them to interact with receptors and other transport proteins [7]. The number of apolipoproteins and the volume of cholesterol esters determine the size of HDL particle [8]. HDL_2 and HDL_3 are the main types of high-density lipoprotein found in circulation.

HDL_2 particles are larger and less-dense and have a density ranging between 1.063 g/mL - 1.125 g/mL while HDL_3 particles are smaller and denser and have a density ranging from 1.125-1.21 g/mL. HDL particles are heterogeneous and may carry other lipoproteins such as apo A-II, apo A-IV, apo E, and apo C. Lipid-poor apo A-I, and discoidal HDL particles have pre-β migration while spherical HDL particles have α-mobility.

Pleiotropic Activities of HDL:

- Removal of oxidized sterols and phospholipids [10, 11].
- Endothelial cell protection and vasodilating effects [12, 13].
- Anti-inflammatory properties [14-16].
- Anti-apoptotic properties [15].

HDL Remodelling: There are several proteins, enzymes, and receptors involved in remodeling HDL:

- Apolipoprotein A-I (apo A-I).
- Lecithin cholesterol acyltransferase (LCAT)
- ATP binding cassette transporter class A1 (ABCA1).
- Cholesterol ester transfer protein (CETP).
- Hepatic lipase (HL).
- Phospholipid transfer protein (PLTP).
- Scavenger receptor class B type I (SR-BI).

Apolipoprotein A-I: There are five major lipoproteins found in our bodies: chylomicrons, VLDL, IDL, LDL, and HDL. The high proportion of proteins in HDL make it dense and the smallest of the five lipoproteins [6]. Apolipoprotein A-I (apo A-I) is the most abundant apolipoprotein in HDL making up about 60% of the total volume of HDL. On the other hand, apo A-II is found Apo A-II is found in relatively smaller quantities [8] see **Table 1**. Apo A-I secretion is often the first step in the biogenesis of HDL. Apo A-I is majorly synthesized in the liver, and a small quantity from the intestines then secreted into plasma. This apolipoprotein is involved in the initial stage of HDL synthesis [17]. It can also be dissociated from chylomicrons and very low-density lipoproteins during lipoprotein-mediated hydrolysis of triglycerides. Inter-conversion of HDL_2 and HDL_3 in the presence of proteins such as CETP, HL, and PLTP generates apo A-I to [18, 19]. This apo A-I formed has a high affinity for cholesterol. It acquires cholesterol and phospholipids through cholesterol efflux. Lipolysis of triglycerides also provides additional cholesterol and phospholipids [4].

ATP binding cassette transporter class A1(ABCA1) mediates the transfer of cholesterol on to apo A-I [20, 21]. Lecithin cholesterol acyltransferase (LCAT) converts this unesterified cholesterol into cholesteryl esters to form a hydrophobic core of HDL. ABCA1 enhances apo A-I binding and cell association in endothelial cells [22-24]. Interaction of this lipid-poor apo A-I and ABCA1 triggers cholesterol efflux in macrophages and fibroblasts, which internalize the lipid-poor apo A-I and resecrete it as a lipidated, cholesterol-rich apolipoprotein, in a process known as retroendocytosis [25]. Apo A-I and apo A-II makes up for about 70% and 20% respectively of the apolipoprotein content [26]. Three forms of apo A-I have been identified. The first form exists as a component of spherical, α-migrating HDL particle, while the second form of LCAT which is a component of pre-beta migrating discoidal HDL. This form is rapidly converted, resulting in a very low concentration in plasma. The last form is the pre-beta migrating, lipid-poor apo A-I [26].

TABLE 1: FUNCTIONS AND MOLECULAR WEIGHTS OF VARIOUS APOLIPOPROTEINS

Apolipoprotein	The molecular weight (D)	Functions
Apo A-I	28,000	Activates LCAT The site of HDL binding to SR-BI A major component of HDL (approx..; 60%)
Apo A-II	17,000	Inhibits hepatic lipase The binding site of HDL A minor component of HDL (approx..; 30%)
Apo A-IV	46,000	Activates LCAT Stimulates cholesterol efflux Controls LPL
Apo C-I	6,600	Activates LCAT Inhibits hepatic TGRL uptake
Apo C-II	9,000	Activates LPL Inhibits hepatic uptake of TGRL
Apo D	33,000	Modulates the activity of LCAT
Apo E	34,000	The binding site of HDL Stimulates cholesterol efflux Mobilizes cholesterol in macrophages

Lecithin: Cholesterol Acyltransferase: LCAT is a glycoprotein found in the liver, testes and central nervous system [27], and it mediates the transfer of 2-acyl groups from lecithin to the free cholesterol, forming cholesteryl ester and lysolecithin [28]. The cholesteryl ester formed partitions into the core of a discoidal HDL particle, thus triggers uptake of cholesterol from any cholesterol donor to form pre-β migrating HDL [29]. The LCAT reaction accounts for most of the cholesteryl esters in circulation.

Discoidal HDL is a suitable substrate of LCAT and can accept more cholesterol from the peripheral tissues than other apolipoproteins. Also, cholesteryl esters are hydrophobic, and they migrate from the surface of the particle to the core. This migration results in the transition from discoidal particle to a spherical shaped particle [28].

ATP Binding Cassette Transporter A1: ABCA1 is expressed in liver, lungs, adrenal glands, fetal tissues, and placenta. ABCA1 acts as a rate-limiting step in the biogenesis of HDL [30, 31]. ATP generates the energy needed to transport cholesterol, phospholipids, vitamins, and cytotoxins between different cellular compartments. ABCA1 also facilitates cholesterol efflux to the monomolecular pre-beta migrating, lipid-poor apo A-1.

Targeted disruption of the ABCA1 gene in mice results in almost undetectable levels of HDL-C and apo A-1 [32, 33]. This study suggests that ABCA1 plays an important role in modulating apo A-I binding and cell association. Suppression of ABCA1 in bovine aortic endothelial cells through RNA interference decreases apo A-I binding and cell association [34].

Tangier's disease, a mutation in the functional gene which encodes ABCA1 impairs lipidation causing hypercatabolism of lipid of lipid-free apo A-I and consequently resulting in substantially low HDL-C levels [20, 35, 36]. For example, in patients with Tangier's disease, fibroblasts and macrophages rich in cholesterol do not release free cholesterol and phospholipids to the lipid-free apo A-I [37, 38].

Cholesteryl Ester Transfer Protein: CETP is a hydrophobic glycoprotein produced in the liver, spleen, and adipose tissue. It mediates the mass transfer of cholesteryl esters from HDL to apo B containing lipoproteins such as LDL, VLDL, and IDL in exchange for triglycerides [39]. The exchanged triglycerides form the core of the HDL particle, thus, act as a suitable substrate for hepatic lipase [40]. Moreover, triglycerides have a greater molecular weight than CEs; therefore, HDL particles formed are increased size. In addition, hepatic lipase along with CETP convert larger HDL_2 into smaller and denser HDL_3 particles releasing lipid-free apo A-I and fatty acids that can be taken up by tissues.

Transgenic expression of CETP in mice that naturally lack this protein results in increased HDL levels [41]. CETP has a net effect of reducing HDL-C levels in hypertriglyceridemic individuals because it is thought that the high levels of triglycerides activate CETP which in turn reduces the levels of HDL [42].

Phospholipid Transfer Protein: PLTP catalyzes the transfer of phospholipids from the surfaces of triglyceride-rich lipoproteins to HDL during lipolysis which is a necessary step during remodeling of pre-β HDL particles [43]. PLTP can be found in kidneys, lungs, heart, skeletal muscles, and the brain. It regulates the sizes of HDL particles by converting them into smaller or larger particles [44]. What's more, ABCA1 interacts with PLTP to enhance cholesterol efflux in the body. Therefore, a deficiency in PLTP results in decreased levels of HDL-C and phospholipids [45].

Hepatic Lipase: HL is synthesized in the liver and is bound to the sinusoid capillaries of the liver [46]. It is involved in remodeling HDL and other lipoproteins such as LDL, VLDL, and IDL [47]. Furthermore, HL has a high specificity for phospholipids and triglycerides [48] and consequently, hydrolyzes triglycerides and phospholipids present in larger lipid-rich HDL_2 particles to form smaller HDL_3 particles [49, 50].

Endothelial Lipase: EL is synthesized in the endothelial cells and liver and acts locally at the site of synthesis [51]. It is also expressed in other tissues such as lungs, kidneys, testes, thyroid gland, ovaries, hepatocytes, and placenta [49]. Deleting functional endothelial lipase in mice results in attenuated atherosclerotic lesions [52]. Inhibition of EL in mice increases HDL-C *in-vivo*.

On the contrary, over-expression of EL decreases the levels of HDL-C [53, 54]. EL concentrations are inversely associated with HDL-C levels in people with metabolic syndrome [55].

Scavenger Receptor Class B Type 1: SR-BI is a glycoprotein expressed in the liver, endothelial cells, adrenal glands, ovary, and testes. It mediates selective uptake of HDL cholesteryl esters by the liver [56]. Through its action, the liver takes up lipids too. Over-expression of SR-BI receptors in the liver of mice increases uptake of HDL cholesteryl esters resulting in increased catabolism of the cholesteryl esters and an eventual decrease in HDL-CEs in circulation [57-59]. SR-BI over-expression reduces atherosclerosis [57].

Reverse Cholesterol Transport Pathways: The cholesterol delivered to the liver is broken down into neutral sterols and bile acids. The main pathways of RCT include:

- Direct delivery of HDL-C to the liver *via* SR-BI
- CETP-mediated transfer of HDL-C to the liver
- Esterification of cholesterol by LCAT
- Cholesterol efflux from extrahepatic tissues to the plasma *via* ABCA1

Direct Delivery of HDL-C to the Liver *via* SR-BI: SR-BI receptors are present in the liver. These receptors influence the uptake of HDL-C esters by the liver, with HDL_2 having a better binding affinity than HDL_3 [60]. SR-BI plays a crucial role in cholesterol efflux.

CETP-Mediated Transfer of HDL-C to the Liver: This is an indirect pathway of delivery of cholesterol to the liver. CETP mediates the exchange of cholesteryl ester present on HDL for triglycerides from VLDL and LDL lipoproteins, enriching the apo B containing lipoproteins with cholesterol. The triglycerides present in the HDL particle are then hydrolyzed by hepatic lipase, thus converting the larger HDL_2 particle into the smaller HDL_3 particle. SR-BI receptors then mediate the delivery of HDL_2 to the liver. The cholesterol-rich apo-B lipoproteins then deliver cholesterol to the liver *via* LDL receptors for excretion (See **Fig. 1**).

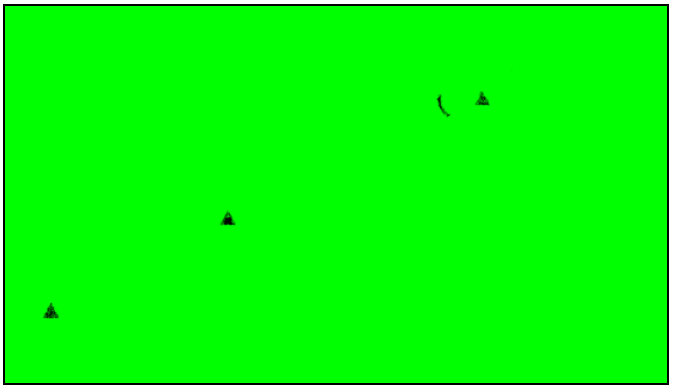

FIG. 1: A SCHEMATIC REPRESENTATION OF HDL-MEDIATED REVERSE CHOLESTEROL TRANSPORT

LCAT-Mediated Esterification of Cholesterol: LCAT esterifies free cholesterol on discoidal HDL, and as a result converts it into spherical HDL particle. Esterification of the FC creates space on the spherical HDL particle which can then take up cholesterol through other pathways such as diffusion, SR-BI, and ABCG1.

HDL can also obtain cholesterol from caveolae and lipid rafts present in the cell membrane, thus the HDL removes cholesterol from macrophages as well. All HDL particles can take up cholesterol.

ABCA1-Mediated Cholesterol Efflux from Peripheral Tissues to Plasma: Apo A-I is synthesized in the liver and secreted in plasma. In plasma, the apo A-I takes up phospholipids to form nascent pre-*β*-HDL. ABCA1 takes up cholesterol present in the cell and delivers it to the cell membrane. The lipid-poor apo A-I then interacts with cellular cholesterol to form discoidal HDL. ABCA1 also mediates the transfer of cholesterol from macrophages to HDL for excretion.

Therapeutic Strategies to Increase HDL Levels: Therapeutic interventions such as the use of CETP inhibitors and niacin have shown a mild increase in HDL-C levels in the blood.

Niacin: Nicotinic acid is the oldest known lipid-lowering agent that acts by reducing the synthesis of VLDL in the liver by its action on Diacylglycerol O-acyltransferase-2 (DGAT-2). Niacin, when used in combination with statin or bile acid-binding resin, increases the cholesterol levels in HDL While it decreases cholesterol in LDL and VLDL [61]. Patients with established coronary artery disease, and were on treatment with high-dose statins, experienced significant

improvements in their lipid profiles when extended-release niacin was added to the statin therapy. However, it is worth noting that these changes in lipid profile were not associated with improved endothelial function [62].

Niacin use has been limited because of its perceived side effects. Laropiprant, a selective prostaglandin D2 receptor-1 antagonist, decreases flushing associated with extended-release niacin. A study in dyslipidemia patients that compared extended-release niacin/laropiprant in doses of 1g-2g showed significantly less flushing than in patients receiving gradually titrated doses of niacin extended-release [63]. Flushing has been reported in more than 90% of the patients who used niacin as part of their lipid-lowering strategy. Other side effects include itching, hyperpigmentation, urticaria and ichthyosis [64].

Low-dose niacin strategy to minimize adverse effects has also been explored in patients with chronic kidney disease. The enrolled patients who had been on a fixed dose of 500 mg/day of niacin for six months were compared to another group of patients who had been taking a statin for 9 months. The niacin group of patients experienced a low frequency of adverse effects with the benefit of significantly raised HDL-C levels and decreased levels of LDL-C at 12 and 24 weeks compared to the baseline level [65].

CETP Inhibitors: Inhibition of CETP increases HDL-C cholesterol, and decreases potentially atherogenic and non-HDL particles, by retention of cholesterol in the HDL fraction. With this concept, CETP inhibitors have been used in clinical trials with the hope that they would increase the levels of HDL-C which in turn would confer protection against atherosclerosis. However, there is lack of direct clinical evidence that raising HDL-C levels translates to protection against cardiovascular events.

In the ILLUMINATE trial, patients received either torcetrapib plus atorvastatin or atorvastatin alone over 12 months. Torcetrapib increased HDL-C levels by 72.1% and decreased LDL-C by 24.9%, but the trial was terminated prematurely because of increased risk of mortality and morbidity by an unknown mechanism [66].

A study evaluated evacetrapib monotherapy or in combination with statins, against statin monotherapy or placebo in 338 dyslipidemia patients. Evacetrapib combination with statins, when compared to placebo or statin monotherapy, increased HDL-C levels and decreased LDL-C levels. Interestingly, a combination of statin and evacetrapib resulted in greater reductions in LDL-C, but not a greater increase in HDL-C when compared to evacetrapib monotherapy [67]. These results are similar to a study conducted in Japanese patients with dyslipidemia, where evacetrapib monotherapy or combination with atorvastatin decreased LDL-C levels and increased HDL-C levels after 12 weeks [68]. Studies evaluating the efficacy of evacetrapib were terminated prematurely because it did not lower the rate of cardiovascular events when compared to placebo [69].

Dalcetrapib, a less potent CETP inhibitor than evacetrapib, was given to patients with low target levels of LDL-C to investigate its effects on endothelial function, lipid levels, and blood pressure. CETP activity after 36 weeks of treatment decreased by 56% when compared to placebo, HDL-C increased by 31% when compared to placebo. On the contrary, LDL-C levels did not change [70].

CONCLUSION: Removal of cholesterol from the peripheral tissues is an important physiological step in the body. Excess cholesterol can accumulate in blood vessels resulting in atherosclerosis. These atherosclerotic plaques pose cardiovascular risks, which could ultimately lead to coronary artery disease, stroke, and myocardial infarction. To prevent or decrease the likelihood of these cardiovascular events, raising the levels of ‘good cholesterol’ with the help of HDL has been a topic of focus in recent research. Many observational studies have shown that raising HDL-C could prevent these events. However, the clinical trials conducted till date has not prevented CVD events by raising HDL-C levels. CETP inhibitors such as evacetrapib, anacetrapib, torcetrapib, and dalcetrapib have been used extensively in clinical trials to raise HDL-C levels and lower LDL-C and triglycerides but have failed to prevent or lower the risk of cardiovascular events. On the other hand, niacin raises HDL-C levels, but its use has been

limited because of flushing. Therefore, further research is needed to understand how HDL and therapies to raise HDL could be used to prevent these events.

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