Chapter 1

Structural Basis and Functional Mechanism of Lipoprotein in Cholesterol Transport

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Abstract

Lipoprotein transports lipids in circulation and is primary driver/modulator of atherosclerosis. Highly dynamics of lipoprotein conformations are crucial to lipid transport along the cholesterol transport pathway, where high-density lipoprotein (HDL), low-density lipoprotein (LDL) and cholesteryl ester transfer protein (CETP) are major players in lipid digestion & transport and the plasma cholesterol metabolism. This chapter covered how do HDL, LDL and CETP induce the metabolisms during cholesterol transport, and summarized recent process in the spatial information of the three lipoproteins, especially the elevations of plasma HDL and LDL, and shine a light on the assembly processes of lipoprotein particles and the substrates dynamics exchanges, for an in-depth understanding on the correlation between various lipoprotein classes and cardiovascular risk.

Keywords: lipoproteins, structure–function relationship, cholesterol transport, reverse cholesterol transport (RCT), lipoprotein particle metabolism

1. Introduction

Cardiovascular disease (CVD), a leading cause of mortality in many developed and developing countries [1], roots in the evolvement of atherosclerosis which is associated with profound disturbances of cholesterol metabolism. To some degree, these metabolism disturbances attribute to the net movement of cholesterol among blood and peripheral tissues. For instance, cellular cholesterol uptake is increased in atherosclerosis, while cholesterol efflux is downregulated [2]. Lipoproteins (consists of apolipoproteins, phospholipid and cholesterol) play an

important role in the transport of cholesterol [3]. Based on density and size, lipoproteins can be classified as ultra-low- (chylomicrons), very low- (VLDL), intermediate- (IDL), low- (LDL), and high- density lipoproteins (HDL) [4]. The last two might be the significant sections of cholesterol transport and metabolism: (1) LDL could transfer lipids into the blood vessel walls, and contribute to the atherosclerosis, which causally be associated with CVD and all-cause mortality; (2) HDL could remove the lipids and carry them back to the liver, being regarded as "good" one [5, 6]. Hence, the lipoprotein-mediated cholesterol metabolism (cholesterol transport) has aroused great attention and showed the benefit for the in-depth understanding of CVDs, as well as the prevention and treatment of CVDs.

As shown in **Figure 1**, the lipoprotein-mediated cholesterol metabolism can be divided into exogenous and endogenous pathways [7]. Exogenous pathway is one of crucial ways to transport cholesterol to the body tissues (chylomicrons → VLDL → IDL → LDL) [8, 9], under the co-action of lipoprotein lipase (LPL) and hepatic lipase (HL) [10, 11]. While the higher plasma LDL level might drive the process of atherosclerosis [12]. Endogenous pathway delivers cholesteryl esters back to the liver, working cooperatively in a concurrent manner with ATP-binding cassette transporter A1 (ABCA1) [13], enzyme lecithin-cholesteryl acyltransferase (LCAT) [14], as well as HDL receptors scavenger receptor B1 (SR-BI) [15] or other unidentified HDL receptor (HDLR) [16]. It is widely accepted that HDL protein particles alleviate atherosclerosis with better cardiovascular health (reverse cholesterol transport, RCT) [6, 17, 18]. Besides, cholesteryl ester transfer protein (CETP) does a heteroexchange of triglycerides and cholesteryl esters between VLDL/ LDL and HDL, with the lessen of cholesterol eliminations [19, 20]. Therefore, the functions of HDL, LDL and CETP play the important roles during the cholesterol transport (lipoprotein particle metabolism), and pharmacological inhibition of CETP is being regarded as a way to prevent CVDs [19, 20].

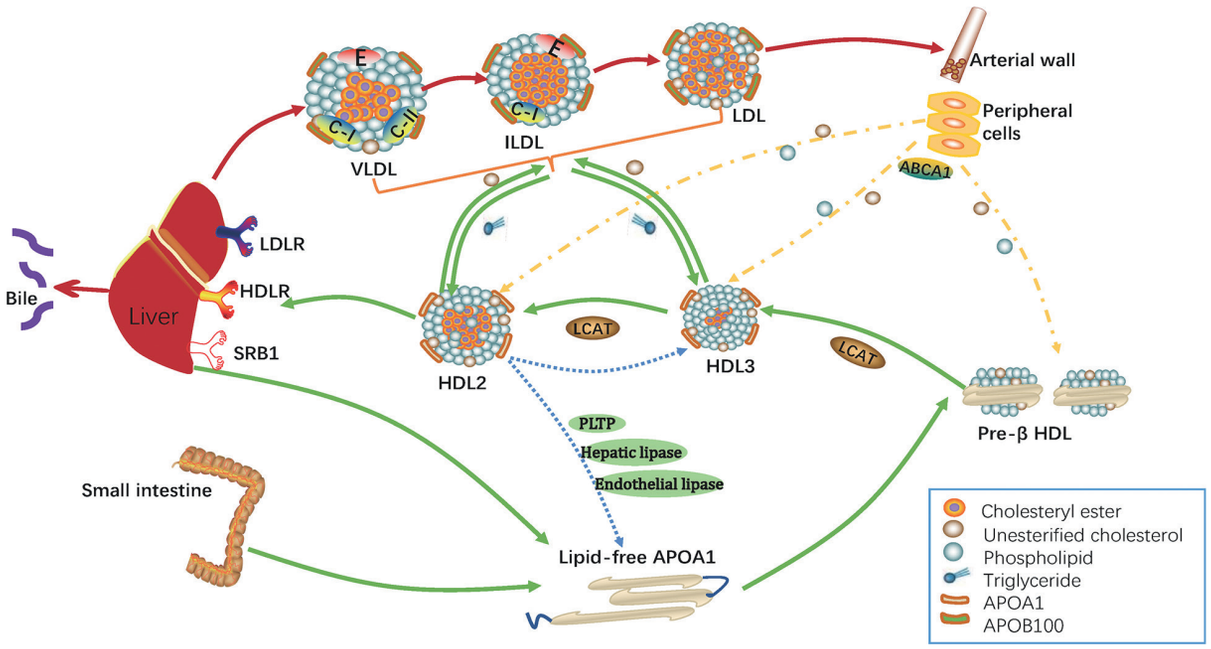

Figure 1. Lipoprotein-mediated cholesterol metabolism in human body.

To best of our knowledge, there are scant reviews elaborating the structure–function relationship of lipoproteins albeit the schematic illustrating is oncoming clear. A comprehensive understanding in this regard was endeavored, and then bioavailability that is closely related with cholesterol transport was discussed. In this chapter, we will summarize the recent achievements towards the structural basis and functional mechanism of lipoproteins in cholesterol transport, mainly focusing on functions of HDL, LDL and CETP, conformation dynamics of lipoprotein particles, and substrates dynamics exchanges.

2. Structure and function of HDL

HDL, a plasma lipoprotein, plays an important role in cholesterol metabolism [21–23], with several potentially anti-atherogenic properties (remove cholesterol from macrophages) [24–26]. Knowing the assembly mechanism and spatial information is of great importance to mediate cholesterol transport. HDLs exit three main steadier state during the cholesterol transport process: lipid-free apoA-I (apoA-I, the major protein component of HDL particles), discoidal and spherical HDL, with highly heterogeneous and differences of density, size, shape, as well as composition of lipid and protein.

2.1. Lipid-free apoA-I

Structure of full-length lipid-free apoA-I (28-kD, 243 residues) at native states still remains unclear due to its high flexibility. The initial X-ray crystal structure revealed that N-terminal truncated (Δ(1–43)) lipid-free apoA-I features "horseshoe-shape" antiparallel helical dimers [27], being regarded as a vital initial model ("double-belt" model) for comprehending the structure of apoA-I on HDL subclasses (**Figure 2b**) [28]. Subsequent crystal organization of lipid-free Δ(1–43)apoA-I accommodated a four-helix bundle [29–31]. However, the structural information is out of step with some physical biochemical measurements, hinting the conformation dynamics of lipid-free apoA-I. The crystal structures of the N- and C-terminally truncated

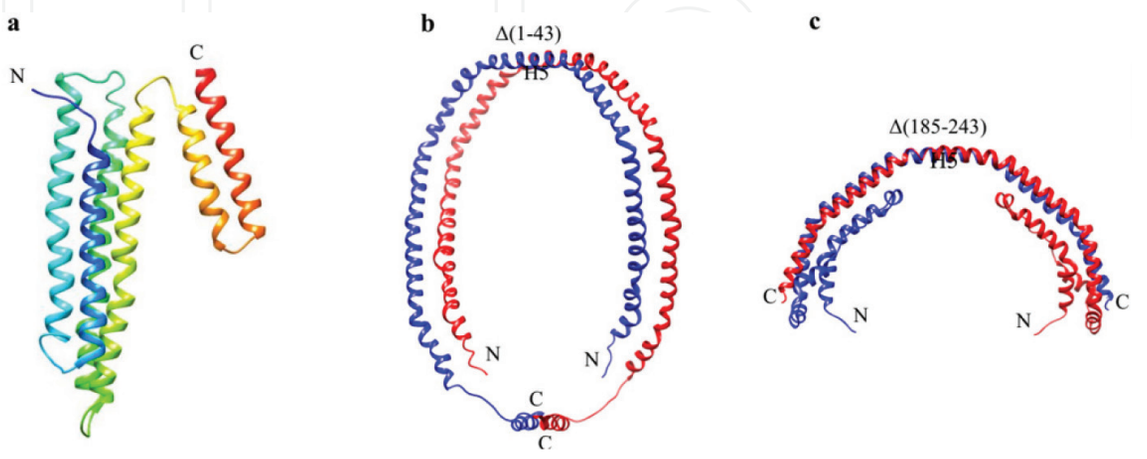

Figure 2. Three structures of lipid-free apoA-I: (a) full-length lipid-free apoA-I, [36] (b) N-terminal truncated Δ(1–43) apoA-I dimer, [27] and (c) C-terminal truncated Δ[185–243] apoA-I dimer [32].

proteins presented antiparallel helical dimers, with inherent properties (e.g., 5/5 repeat register, **Figure 2b** and **c**) in the lipid-bound and intermediate states [27, 32]. Amphipathic α-helix enables apoA-I to stabilize all HDL subclasses via the conformation change, and N-terminal two thirds constitute a dynamic, four-helix bundle, and the helical segments unfold and refold in seconds. While the C-terminal third, an intrinsically disordered domain, mediates initial binding to phospholipid surfaces. These structural motifs are important for the remodeling of apoA-I during the formation of various HDL particles. Nowadays, there remains some confusions for the structure of full length free apoA-I, especially the dynamic conformations in solutions. The dynamic helical structure is unfolding and refolding in seconds, and the helices bundle at the N-terminal of apoA-I is far more stable than could be achieved in isolation, with mutually stabilizing interactions [33, 34]. The highly dynamic apoA-I molecules are capable of adopting an array of conformations through remodeling HDL that is crucial to lipid transport during the RCT process. Further studies show that mutations in apoA-I induce varied types of dyslipidemias [35].

2.2. Discoidal HDL

Human plasma HDL is high heterogeneous, and exists as a short-lived heterogeneous substrate for LCAT in human plasma. Hence, reconstituted HDL particle (rHDL) is a powerful in vivo model system to study its structure and function, with most of the properties of native lipoprotein complexes (e.g., LCAT activation, lipid transfer, and receptor binding) [37–39]. Based on the crystal structure of Δ(1–43)apoA-I, [27] the original double-belt model features two antiparallel monomers, where each helix 5 segments directly oppose each other [40, 41], and the closely contact involved hydrophobic face of amphipathic α-helix with the fatty acid acyl chains [42]. In refined "looped belt" model, N- and C-terminal 40–50 residues doubled back as the "belt and buckle" [43], and residues 134–145 were coincide with a looping region, resulting in partial opening of the parallel belts. It is consistent with the accession between LCAT and the cholesterol and phospholipid acyl chains [44], With the aid of mass spectrometry (MS) and rHDL, lipid-free and lipid-bound apoA-I structures were solved at 104 Å resolution, and resulted in a "solar flares" model, where C-terminal of both apoA-I molecules interacted with each other, and 159–178 loop might be the LCAT binding site, with reduced deuterium exchange [45, 46], Different from normal discoidal shape, double superhelix (DSH) apoA-I model [47] has an open helical shape, with the similar interface interaction between two apoA-I molecules (5/5 double-belt). While, the DSH model is not stable, and could rapidly collapse to a disc-shaped structure during the molecular dynamics (MD) simulations [48].

In according to the rapid growth of transmission electron microscopy (EM) technique, the directly imaging particle's structure can be performed on individual particles, in order to preferably investigate lipoprotein structures. Negative stain EM combined with cryo-EM tomography have been applied to uncover the discoidal shape of apoA-I/HDL particles (both plasma HDL and 7.8, 8.4, 9.6 nm of rHDLs) [49, 50]. In these rHDL particles, the double belt was formed in an antiparallel fashion, with a gross "right-to-right" rotation of the helices after lipidation. The nonhelical regions in lipid-free apoA-I (residues 45–53, 66–69, 116–146, and 179–236) change conformation from random coil to α-helix, to adjust a hydrophobic interior

[34, 46]. Above descriptions were further confirmed by the structures of reconstituted discoidal HDL particles via nuclear magnetic resonance (NMR), electron paramagnetic resonance (EPR) and transmission electron microscopy (TEM) methods [51]. Based on the structures of lipid-free and lipid-bound apoA-I, we can speculate that the monomeric apoA-I forms a helix bundle in which the C-terminal domain binds the lipid to form a helical structure (**Figure 3**). Discoidal HDL are stabilized by two apoA-I molecules wrapped around the edge of the disc in an antiparallel, double-belt arrangement so that the hydrophobic PL acyl chains are protected from exposure to water [52]. These apoA-I molecules are in a highly dynamic state and adapt to discs of different sizes by certain segments forming loops that detach reversibly from the particle surface.

2.3. Spherical HDL

Due to the complexity of spherical HDL particles in human plasma, the spherical HDL structures are rarely known compared with lipid-free apoA-I and discoidal HDL. Recent developments in native and reconstituted spherical HDL supported a trefoil model, using by the elegant chemical cross-linking and mass spectrometry [53]. In this model, half of each apoA-I molecule in the double-belt arrangement is bent 60° out of the plane of the particle, suggesting the hinging of the Δ(1–43)apoA-I molecule is occur near residues 133 and 233 [53] which is different from the hinging of the full-length protein conformation, meanwhile, trefoil model is assumed to occur near residues 65 and 185 [54]. Determined by small angle neutron scattering method, the helical dimer with a hairpin (HdHp) model was proposed, associated with the intramolecular interactions within the hairpined apoA-I [55].

The first LpA-I HDL model at molecular level was proposed, with only apoA-I fractions isolated from human plasma [56]. These isolated human plasma HDL particles range in diameter from 8.8 to 11.2 nm and contain 3–5 apoA-I molecules. It was found that apoA-I adopts intermolecular interactions in plasma HDL which is very similar to those of the double-belt and trefoil models derived from reconstituted systems. Thus, apoA-I might adopt a common structural organization, characterized by distinct intermolecular contacts, regardless of size and shape or natural versus synthetic method of production [57]. Furthermore, circulating

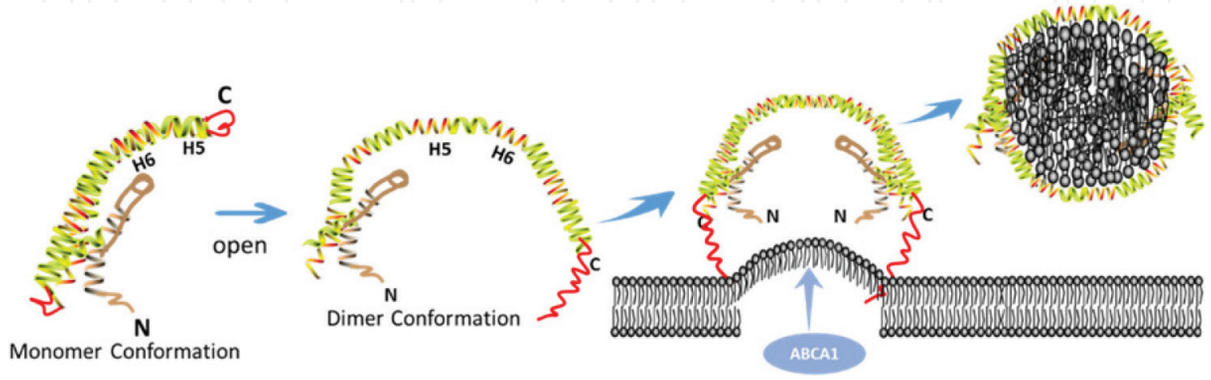

Figure 3. The monomer open conformation transfer to dimer conformation of apoA-I (intermediate state) and final HDL state in solution regulated by the H5 region.

sHDL contains similar amount of core lipid in reconstituted sHDL and has obviously less surface lipid monolayers, indicating that the apoA-I package on native spheres is much closer than the typical recombinant particles [46]. When a HDL disc alters to a sphere (LCAT converts free cholesterol to cholesteryl ester), global apoA-I conformation does not change significantly between particles of different shapes or origins, with similar protein–protein contacts.

3. Structure and function of LDL

In normal human body, there are about 70% plasma cholesterol contained in LDLs, and the endocytosis of cholesterol-rich LDLs is mediated by LDL Receptor (LDL-R) on the surface of body cell. Hence, LDLs work as the vehicle for cholesterol transportation between liver and cells to maintain a constant cholesterol supply in human body [58, 59]. In some abnormal conditions, LDL might induce over-accumulation of cholesterol to form foam cells, resulting in the development of atherosclerosis [60]. The apo-B48 (apoprotein B48) and apo-B100 (apoprotein B100) located in surface of LDL particles tend to interact with extracellular material, which make LDL particles easy to bind with blood vessel intima [61]. The oxidation-LDL can promote lipoproteins aggregation [62, 63] and provoke inflammation by recruiting the circulating monocytes to the site followed invade the vessel wall and differentiate into macrophages, to finally produce atherosclerotic plaque [62, 64–66]. Cryo-EM combined with single particle technology and small angle scattering model reconstruction technology have been effectively applied to analyze the LDL structures, and molecular components [67]. LDLs include difference in density (~1.019–1.063), shape, size (diameter ~18–25 nm), surface charge and chemical composition [68]. A general consensus is that LDLs particles all have two compartments, an amphipathic surface phospholipid monolayer which surrounded by one single copy of apoB-100, and a hydrophobic lipid-cholesteryl esters core [69]. The structure and physical function of LDLs predominantly depend on the core-lipid composition and the conformation of the apoB-100 [70, 71].

3.1. Lipid core of LDL

Lipid core of LDL mainly consists of cholesteryl esters, some triglycerides, and some free-cholesterol. Structural changes of LDL are strikingly related to physiological temperature [72]. Lipids located in core show order arranged to a liquid-crystalline phase below the critical temperature, indicated by the results of X-ray and neutron small angle scattering technology, with the transition temperature of 15~35°C [73, 74]. Besides, the overall structure of LDL is a classical spherical particle when core structure is composed of radial cholesteryl esters arranged into a concentric spherical shell [75, 76]. However, the core-located lipids present in the liquid-crystalline state within an ellipsoidal shape particle revealed by the cryo-EM data [76, 77]. It seems reasonable to speculate that the change of temperature might indirectly change the shape of LDL particles from roughly spherical to ellipsoid [67]. Many efforts have been made to explore the structure of LDL at different temperatures, such as 4, 6 [77–79] and 37°C [80].

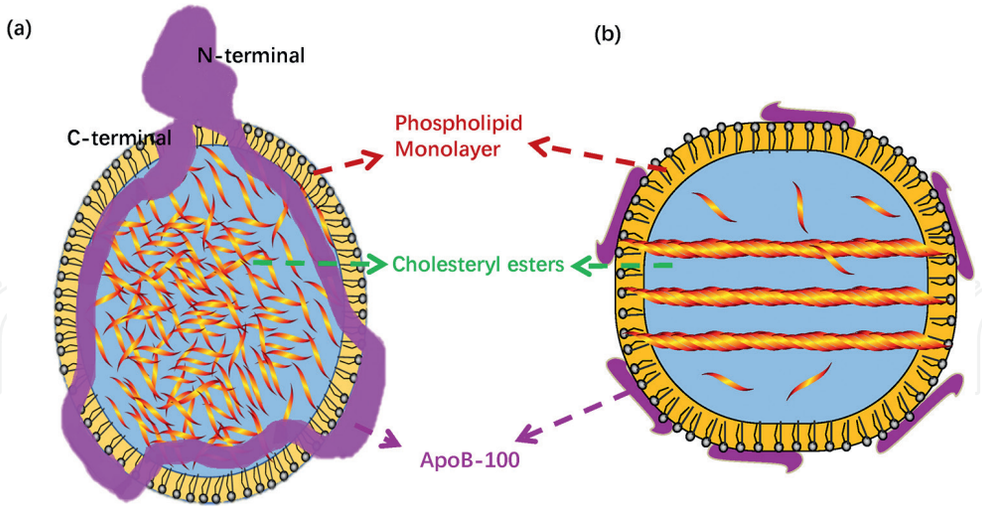

Figure 4. Overall structure and core structure of LDL above (a) or below (b) the critical temperature.

3.2. apoB-100 in LDL

ApoB-100 (4536 residues, ~20% of overall LDL) is the only protein component of LDL, and wrapped around the phospholipid monolayer on the surface of LDL particle, with an irregular ring shape. N- and C-terminus of apoB-100 touch each other, with the formation of a protruding globular structure at N-terminal [81]. A more generally accepted structural model of apoB-100 is "pentapartite" structure, which generated by molecular simulations. In this model, apoB-100 has five consecutive functional domains, NH2-βα1-β1-α2-β2-α3-COOH [79]. As shown in **Figure 4**, a new LDL reconstruction in which lipid core is revealed an organized three-layer structure by using the single particle approach, including a pair of "paddles" configurations with several long "fingers" extensions which have similar length and interval [82].

4. Structure and function of CETP

CETP acts as a medium between lipoproteins for elevating plasma LDL-C (or VLDL-C) level and lowering HDL-C level [19]. A series of CETP inhibitors have been investigated in clinical, such as torcetrapib, dalcetrapib, evacetrapib, and anacetrapib [83–85]. However, current inhibitors represent the turbulent beginning of CETP inhibition and an increased mortality rate related to off-target effects and lack of efficacy [86–88]. Accompanying adverse effects call for a deeper exploration of the mechanism for CETP-mediated lipid transfer.

CETP is a hydrophobic transfer protein composed of 476 amino acids and reveals a so-called banana-shape (the size is 135 × 30 × 35 Å, see **Figure 5**) [20]. Its crystal structure includes two different β-barrel structures in N- and C- terminal respectively, and a central β-sheet with an ~60 Å-long hydrophobic central cavity, which can hold two phospholipids and two cholesterol molecules. Moreover, the two phospholipid molecules that located in two pores near the central domain expose the hydrophilic terminal to the aqueous environment and hydrophobic terminal to the hydrophobic cavity. Because of its special function to transfer cholesterol

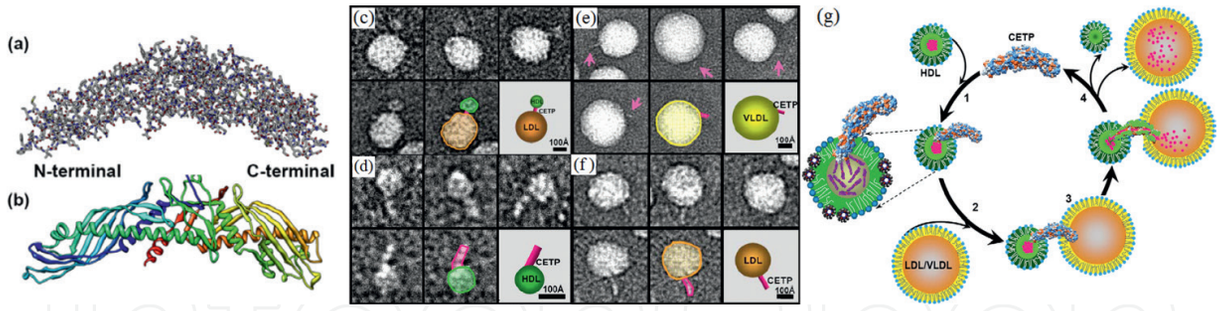

Figure 5. The crystal structure of CETP (PDB: 2OBD) and three-dimensional density maps of CETP binging lipoproteins. (a) Atom figure of CETP. (b) Secondary structure of CETP. (c) Ternary complexes of HDL-CETP-LDL in cryo-EM micrographs. (d)~(f) the CETP insert into HDL, VLDL, LDL respectively in cryo-EM micrographs. (g) (color online) the tunnel model of CETP-mediated lipid transfer [89].

esters between HDL and LDL (or VLDL), the way of CETP interacts with lipoproteins is extremely essential. CETP shows a high binding affinity for nascent HDL and other lipoproteins to cover the lipoproteins surfaces owing to its proper curvature radius. They proposed a lipid transport mechanism, shuttle model. In this mechanism, the CETP in turn covers the surface of LDL (or VLDL) and HDL to swap LDL-cholesterol esters (or VLDL-cholesterol esters) with HDL-triglycerides. These steps are constantly recycled until the completion of the transport process, in which cholesterol esters move from LDL (or VLDL) to HDL [20]. This model based on the hydrophobic cavity of CETP and its feasibility of binding to lipoproteins, explains the mechanism of CETP-mediate lipid transfer reasonably, but there are not complex of CETP binding to lipoproteins in the cryo-EM micrographs intuitively to verify the authenticity of the model.

Zhang et al. [89] studied human recombinant CETP with cryo-EM by using an optimized negative-staining (OpNS) EM protocol [49, 90]. Applied the single-particle techniques, they obtained the 3D structure of CETP and the complexes of CETP binging to lipoproteins. In the 3D-map of complexes, they discovered the HDL-CETP binding structure which appears to be formed by N-terminal of CETP insert into HDL and the HDL-LDL (or HDL-VLDL) is formed by C-terminal of CETP insert into HDL (or LDL) (**Figure 5**c~f). This conclusion was later confirmed by Geraldine et al. by using large-scale atomistic molecular dynamics [91]. The measurement of the protrusion from the lipoproteins surface shows that ~48 Å of the tapered N-terminal end of CETP penetrates the HDL surface and ~25 Å of the C-terminal end of CETP penetrates the LDL surface (~20 Å of the C-terminal end of CETP penetrates the VLDL surface) reaching the lipid–rich, lipoproteins core. Furthermore, Zhang et al. proposed the tunnel model of lipid transfer mediated by CETP [89, 92, 93]. In this model, both CETP terminals finish penetrating surface sites on lipoproteins, N-terminal to HDL and C-terminal to LDL (or VLDL). Then neutral lipids, including cholesterol esters and triglycerides, transfer through the hydrophobic tunnel at the core of the CETP (**Figure 5**).

However, there are some discrepancies with the tunnel model mentioned above. Matthias et al. used the experiments which involve three monoclonal antibodies to demonstrate that the antibodies binding on both ends of CETP do not inhibit CETP's function of transshipment cholesterol esters, but the antibodies on the middle does [94]. In their research they supposed that the formation of the ternary tunnel complexes is not a mechanistic prerequisite by CETP

to perform its functions. Hence, the real mechanism of CETP-mediated lipid transfer still remains to be studied and verified.

5. Conclusion

In this chapter, we briefly summarized the functional mechanism and structural basis of lipoproteins (e.g., HDL, LDL and CETP) in cholesterol transport, as well as their structural dynamics during the transport process. Furthermore, the latest developments in the plasma lipoprotein (HDL and LDL) elevations were summarized, especially the conformational changes of lipoprotein particles. Due to the incapability of the current assays and highly heterogeneous of lipoprotein particles, the function of lipoprotein in cholesterol transport remains elusive with regard to many important questions, such as how the lipoprotein particle assembles and how the assembly modulates the neutral lipids dynamic exchanges at the molecular level. Cryo-EM coupled with MD simulations have revealed several important mechanisms of CETP-mediated lipid exchange and metabolism with all-atom detail [89, 95]. Further researches could pay more attention to simultaneously monitor the dynamic structural change of lipoproteins and the dynamic mechanism of lipid transfer, especially the internal motivation of physical mechanism during the process of lipid transport.

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Conflict of interest

The authors have declared that no competing interests exist.

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