MINIREVIEW

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The Structure of Apolipoprotein A-I in High Density Lipoproteins*

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Not long ago, high density lipoproteins (HDL)[2] were second class citizens with regard to therapeutic strategies for lowering the risk of atherosclerosis and coronary artery disease (CAD). To date, most successful approaches have focused on the better understood pathways of cholesterol synthesis and low density lipoprotein (LDL) production, the "forward" cholesterol transport pathway. For example, the statin class of cholesterol synthesis inhibitors significantly reduces LDL levels resulting in a less atherogenic plasma lipoprotein profile. However, the relatively modest improvements in mortality conferred by these drugs suggest that other factors also play significant roles in defining CAD risk. The recent discoveries of HDL-interacting cell surface proteins such as scavenger receptor BI (SR-BI) and ATP-binding cassette transporters A1 (ABCA1) and G1 (for recent reviews see Refs. 1 and 2) have helped define the steps of reverse cholesterol transport (RCT), *i.e.* the movement of cholesterol from the periphery to the liver for catabolism (3, 4). Additionally, there is growing evidence that HDL anti-inflammatory properties may contribute significant protective effects (5), apparently via specific cell signaling pathways (6). These discoveries have fueled a new interest in HDL as a target for CAD treatment (7). Unfortunately, a complete understanding of HDL function has been hampered by a lack of information on its structure and the molecular basis of its interactions with other proteins. This review summarizes the latest efforts in understanding the structure of the defining protein component of HDL, apoA-I, in the various stages of the RCT pathway.

HDL Protein Composition

ApoA-I comprises roughly 70% of the HDL protein mass and apoA-II another 15–20%. The remainder is made up of amphipathic proteins including the apoCs, apoE, apoD, apoM, apoA-IV, paroxonase and many other proteins as identified in a recent proteomics study (8). These lower abundance proteins are not present on all HDL particles and may actually be sequestered on compositionally distinct particles within the density class. These amphipathic proteins form stable micellar complexes with phospholipids, cholesterol, triglycerides, and cholesteryl esters. In humans, HDL exists predominantly as two major density species, HDL_2 (d = 1.063–1.125 g/ml) and HDL_3 (d = 1.125–1.210 g/ml) with diameters ranging from 70–120 Å. Minor, but clearly important, subspecies include lipid-poor apoA-I and nascent discoidal particles. In addition to density, HDL can be separated by major apolipoprotein species using immunoaffinity chromatography into apoA-I-containing particles that lack apoA-II (LpA-I) and those that contain both apoA-I and apoA-II (LpA-I/A-II) (9). Several functional distinctions have been proposed for these species, with apoA-II thought by some to be proatherogenic. However, there are also many examples of antiatherogenic properties of apoA-II (see Ref. 10 for a review).

As it comprises the majority of the protein mass, structural studies of human plasma HDL must first focus on apoA-I. ApoA-I is a 243-amino acid, 28-kDa single polypeptide that lacks glycosylation or disulfide linkages. Aside from the N-terminal 44 amino acids, the apoA-I sequence appears to be organized into eight α-helical segments of 22 amino acids and two 11-mer repeats that are frequently separated by proline residues (11). These helices are predicted to be amphipathic, with a hydrophobic face that likely mediates lipid interactions and a polar face that interacts with water. The thermodynamic drive to minimize the aqueous exposure of these hydrophobic surfaces is probably the major mediator of protein folding, whether these surfaces are present in a lipid-free state in which the nonpolar helical faces sequester within the protein or in the lipidated state where they likely contact aliphatic regions of lipid assemblies. More information on how amphipathic helices mediate apoA-I lipid binding can be found in recent work from the Phillips laboratory (12) and in the excellent review series by Brouillette *et al.* (13).

Lipid-free ApoA-I

About 5–10% of human plasma apoA-I exists in a lipoprotein-unassociated state. This fraction likely derives from direct secretion by the liver/intestine or by dissociation from HDL or triglyceride-rich lipoproteins (14). Lipid-free apoA-I has garnered significant interest of late because the absence of lipid appears to be a requirement for the interaction of apoA-I with the ABCA1 transporter, a key reaction for the maintenance of plasma HDL levels (2). Currently, there is no strong consensus as to whether this fraction is truly lipid-free or if it contains trace amounts of lipid (lipid-poor). Most structural studies have focused on apoA-I that has been completely delipidated by various means; it can thus be studied in aqueous solution. Under these conditions, apoA-I forms a heterogeneous population of oligomers from monomers to pentamers in a concentration-dependent manner. As a further complication, apoA-I has been proposed to exhibit characteristics of a "molten globule" with defined elements of secondary structure, but it may contain regions lacking defined tertiary structure (15, 16). The reader is referred to the recent works of the Atkinson (17) and Gursky laboratories (18) for information on apoA-I folding thermodynamics.

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[2] The abbreviations used are: HDL, high density lipoprotein; LDL, low density lipoprotein; CAD, coronary artery disease; RCT, reverse cholesterol transport; apo, apolipoprotein; ABCA1, ATP-binding cassette A1; FRET, fluorescence resonance energy transfer.

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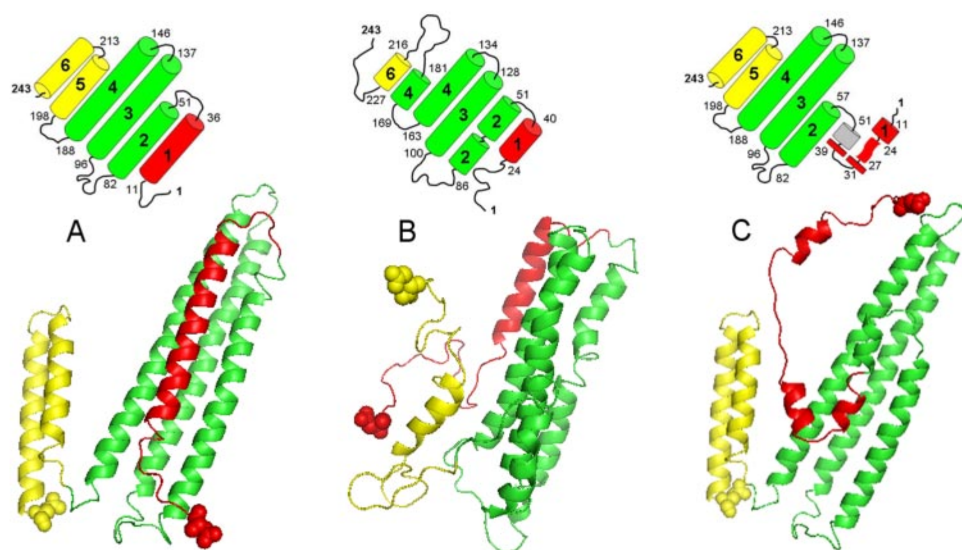

FIGURE 1. **Models of full-length lipid-free apoA-I.** *A*, x-ray crystal structure of lipid-free apoA-I by Ajees *et al.* (20). *B*, an independently generated homology model of full-length lipid-free apoA-I by cross-linking and sequence threading techniques (25). *C*, a modification of the Ajees crystal structure in which the secondary structure of the N-terminal 98 residues was modeled according to the EPR data of Lagerstedt *et al.* (28). For all models in this figure, the N-terminal 44 residues are colored *red*, the C-terminal 50 residues are colored *yellow*, and the extreme terminal amino acids are shown as space-filled. The *insets* show the elements of secondary structure as if they had been laid flat with no tertiary relationships. A short run of the β-sheet in the N terminus of the Lagerstedt model is shown as an undulating sheet.

Despite the challenges posed by apoA-I dynamics, two groups have successfully crystallized apoA-I. In 1997, Borhani *et al.* (19) crystallized a deletion mutant lacking the N-terminal 43 amino acids. The structure at 4 Å resolution showed a ring-shaped assembly of four apoA-I molecules arranged in extended, kinked α-helices. However, because of the missing N terminus and the tetramerization, the structure appeared to be more applicable to lipid-bound rather than lipid-free apoA-I (see below under "Discoidal HDL"). In 2006, full-length lipid-free apoA-I was crystallized by Ajees *et al.* (20) in the presence of chromium tris-acetylacetonate. The structure (Fig. 1*A*) indicated that the N-terminal two-thirds of the molecule is involved in an intramolecular four-helix bundle organization, reminiscent of the crystal structures of monomeric apoE (21) and the insect apolipophorin III (22). However, the apoA-I four-helix bundle is likely of moderate stability, as the number of H-bonds per residue is only 0.71 compared with 1.03 for apoE. Interestingly, the C-terminal 50 amino acids form an independent hairpin domain that interacts with the corresponding regions of two other apoA-I molecules in the crystal. This organization appears to confirm previous proposals that apoA-I adopts a structural and functional domain organization in which the C terminus mediates lipid interactions with subsequent unfolding of an N-terminal helical bundle (23, 24). Furthermore, the structure is generally consistent with one proposed a year earlier using homology modeling and chemical cross-linking (25). The homology model proposed a four-helix bundle in the N terminus with turns between helices 1, 2, and 3 that are quite similar to the crystal structure (Fig. 1*B*). Both models also clearly show that the helices of the bundle are not always punctuated by the proline residues originally thought to demarcate the 22-amino acid amphipathic helices. Helix 4 in the homology model is terminated near residue 165 and doubles back on the helical bundle, whereas the crystal structure shows one contiguous helix. Beyond that, both models show the C-terminal residues from about 186 to 191 form a separate C-terminal domain, albeit much less organized in the homology model.

Although the Ajees crystal structure appears to be consistent with some data generated via lower resolution techniques as described above, it should be pointed out that the model is inconsistent with several well established observations. One of the obvious differences between the models in Fig. 1 is the total helical content. The crystal structure puts apoA-I at about 83% helical, a much higher content than the 50–57% typically found for monomeric apoA-I by circular dichroism (26, 27). The homology model puts apoA-I at a more reasonable 56% helicity, although some areas were assigned as random coil simply because of a lack of a suitable homology template for those regions. The crystal structure shows that the N-terminal 43 residues are almost entirely helical, whereas most of this region is random coil in the homology model. A similar statement can be made for the 50 or so residues at the C terminus. A recent study by Lagerstedt *et al.* (28) examined the secondary structure of the first 98 residues of lipid-free apoA-I by EPR. They concluded that this region does indeed contain helical residues, but the helical stretches are short with periodic breaks in contrast to the crystal structure. Interestingly, these investigators showed evidence for a short run of β-strand between residues 20 and 25. Using this information, they presented an alternate model based on the crystal structure with the N terminus in an alternate conformation (Fig. 1*C*). This same group had demonstrated that the C-terminal 78 residues were also significantly less helical than implied by the crystal structure, with only about 43 of those residues in helices (29). A second short run of β-strand in the C-terminal region was also not apparent in the crystal structure. Additionally, the crystal structure shows that the four tryptophan residues present in the N terminus of apoA-I are surprisingly exposed to solvent, particularly Trp-8 and Trp-50. This is in contrast to fluorescence data obtained with monomeric apoA-I under physiological buffer conditions (30) showing a hydrophobic environment for these residues. Finally, our analysis of the crystal structure shows that the C-terminal portion of the helical bundle exhibits significant hydrophobic contacts, consistent with a stable bundle. By contrast, the N-terminal portion, especially helix 1, exhibits contacts that are tenuous at best.

Together, these data suggest that the rough placement of the four helical bundle is probably correct in the homology and the crystal structure models in Fig. 1. However, in true solution, the

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N- and C termini are probably not folded into the nice clean helical packages apparent in the crystal structure. A key question that remains is whether the two termini might interact to modulate the ability of apoA-I to bind lipids as suggested by Rogers *et al.* (16) and supported by Fang *et al.* (31). It should be kept in mind that the crystal was generated at high concentrations (3 mg/ml) in salt with 10% polyethylene glycol and a stabilizing agent. It is likely that the crystal structure represents a minimum energetic conformation that apoA-I is capable of adopting, at least under crystalization conditions. However, it does not adequately reflect the dynamics of particular regions under physiological conditions. The homology model, although generated from data obtained under physiological conditions, suffers from its reliance on a limited set of cross-links and a paucity of structural templates. Despite their flaws, however, both models are valuable as a foundation for *in silico* molecular dynamics studies designed to simulate more native conditions.

We would argue that the dynamic nature of apoA-I makes the expectation of a single "perfect" structure unrealistic. The protein likely exists as a constellation of related and interconverting species. The utility of the models in Fig. 1 will ultimately lie not in defining some static location of each residue but in identifying which regions are most likely to undergo conformational transitions in response to lipid or upon contact with cell surface proteins such as ABCA1.

Discoidal HDL

Discoidal HDL are generated by exposure of lipid-free apoA-I to the cholesterol/phospholipid transfer activity ABCA1. They are excellent substrates for lecithin:cholesterol acyl transferase, and the resulting conversion of free cholesterol to cholesteryl ester rapidly converts the discs to the spherical forms commonly found in plasma. A detailed knowledge of apoA-I structure in discs is important for understanding the molecular life cycle of HDL. Being short-lived, they are not easily isolated from plasma, although small amounts can be detected in extra-plasma compartments such as peripheral lymph. Fortunately, methods have been developed to reconstitute discs *in vitro* with high yield and purity (32), and the resulting (r)HDL particles have been studied extensively. The best characterized particles have a hydrated diameter of 96 Å containing two molecules of apoA-I with 150–160 molecules of phospholipid. Segrest (33) proposed in the late 1970s that the α-helices of apoA-I wrap around the circumference of discoidal patch of a phospholipid bilayer with the long helical axis perpendicular to the acyl chains, *i.e.* the "belt" model. Alternatively, the "picket fence" model holds that the 22-amino acid helical repeats, punctuated by turns centered on the repeating proline residues, could traverse the bilayer edge parallel to the acyl chains (33, 34). The Borhani crystal structure (19), despite lacking lipid, depicted apoA-I in a ring shaped oligomer with no sign of hairpin turns, implying that apoA-I may prefer a belt-like orientation in lipoproteins. Since then, there have been two studies on true lipid-containing particles that specifically addressed the orientation of apoA-I helices in relation to phospholipid acyl chains. The first was attenuated IR experiments by Koppaka *et al.* (35) that clearly supported the belt model in hydrated particles. More recently, this methodology demonstrated that apoE (36) and apoA-II (37) also adopt a belt-like orientation in particles of similar morphology. The second study involved fluorescence depth measurements of probes on each helix that also supported the belt model for apoA-I (38) as well as for apoE (39).

With the question of helical orientation addressed, attention focused on determining the spatial relationships between molecules of apoA-I on a disc. The belt model with the best theoretical support is the "double belt" model in which each of two ring-shaped apoA-I molecules wraps around a patch of phospholipid bilayer, each on its own leaflet, in an antiparallel orientation (13, 40, 41). Computer analysis predicted a registry between the monomers with similar intermolecular salt bridge connections implied by the Borhani crystal structure. In this model, helix 5 of each apoA-I molecule lies in direct opposition (5/5 orientation, Fig. 2*A*). An alternative belt model (11) proposed two possible hairpin orientations, where each molecule interacts with both leaflets after a turn. This allows salt bridge interactions similar to the double belt, although they are intramolecular in the hairpin.

The similarity in potential salt bridge patterns between the hairpin and belt models initially led to some difficulty in defining tertiary relationships. Studies using fluorescence resonance energy transfer (FRET) clearly ruled out the picket fence model but were consistent with helix 5-to-helix 5 contact (5/5) between the molecules in either the belt or hairpin model (42). Other studies using similar methodologies suggested mixtures of head-to-head

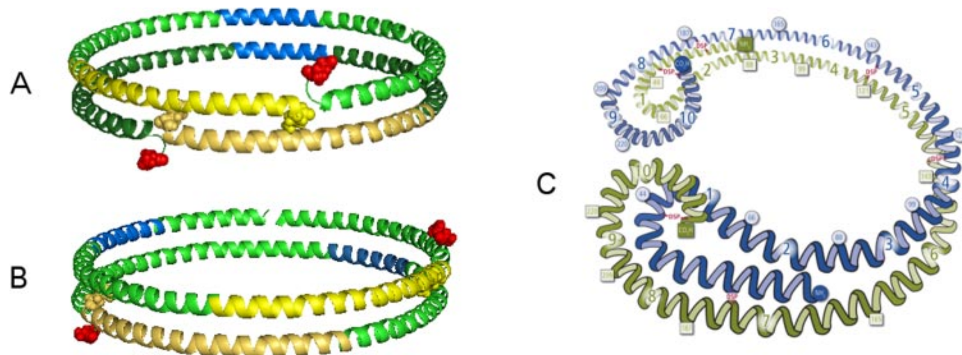

FIGURE 2. **Three recent models for discoidal reconstituted HDL particles containing two molecules of apoA-I.** *A*, the Segrest 5/5 double belt model (40). The model shows two molecules of apoA-I, one on top and one on the bottom, that surround a patch of phospholipid bilayer (not shown). This model was built using the Δ1–43 deletion mutant of apoA-I. The N-terminal amino acid 44 is shown in *red* space-fill form, and the C-terminal 50 amino acids are in *yellow* with the terminus in *yellow* space-fill. Helix 5, the point of overlap of the two molecules, is indicated in *blue*. *B*, the Silva 5/2 rotamer of the double belt model (25). The features are presented in the same color scheme as given for *A*. Note the shifted positions of helix 5 (*blue*) and the termini of both molecules. *C*, a modification of the 5/5 double belt model proposed by Bhat *et al.* (45). The two molecules of apoA-I are shown in different colors with intermittent amino acids *numbered* in *boxes* and *circles*. The N-terminal 44 amino acids are proposed to double back to interact with the C-terminal region of the opposing apoA-I molecule on the disc edge.

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and head-to-tail hairpins (43). More recently, we applied a cross-linking approach to discoidal HDL particles containing two molecules of apoA-I (44). The result was nine intermolecular distance constraints that strongly supported the double belt model in particles with two molecules of apoA-I. This study also implied that a shifted (5/2) registry of the resident apoA-I molecules could also exist (Fig. 2*B*), possibly in dynamic equilibrium with the 5/5 form. The functional implications for such a conformational shift are intriguing and open the possibility that different rotamers may interact with distinct plasma factors to modulate HDL metabolism. A subsequent study used a very similar approach to find three intermolecular cross-links (45), two of which were consistent with the 5/5 double belt model. Interestingly, the authors interpreted a third cross-link to indicate that the apoA-I N terminus forms a hairpin turn centered around residue 44 in order to interact with the C-terminal portion of the second apoA-I molecule that has also doubled back on itself (Fig. 2*C*). This organization differs in that it no longer forms a closed loop encapsulating the lipid bilayer. Instead, the two molecules form an open-ended structure reminiscent of a pair of earmuffs. This twist on the double-belt model may have implications for the addition of other apolipoproteins to HDL particles. Of note, our analysis indicates that this third cross-link is also quite consistent with the shifted 5/2 double belt proposed by Silva *et al.* (44), shown in Fig. 2*B*.

Taking a different approach, Martin *et al.* (46) used FRET to study apoA-I mutants with single tryptophan donors and acceptor probes attached to introduced cysteine residues in reconstituted HDL discs. The data clearly showed that apoA-I forms an extended antiparallel conformation with a registry consistent with the double belt model. In the same study, electron paramagnetic resonance experiments further suggested that region 134–145 may be a flexible loop that may modulate changes in particle size, an observation consistent with previous proposals of a hinge domain near this sequence.

The sum of the available data on these simple reconstituted discs shows that apoA-I can clearly adopt an organization that resembles the 5/5 double belt model as depicted in Fig. 2*A*. However, it is also clear that there is potential for significant conformational adaptability within this general framework, particularly at the termini and in the middle of the apoA-I molecules. Although the picket fence model appears to have fallen out of favor, the hairpin models remain worthy of continued consideration. If one assumes that there is room for only two helices lying parallel around the edge of a disc, then the addition of a third molecule of apoA-I to these discs requires that it adopt a distinct conformation from the first two. A conceptually straightforward way to do this is to invoke the hairpin organization for at least one apoA-I molecule in discs that contain three apoA-I polypeptides (40). More work will be required to tackle this intriguing issue.

Spherical HDL

Spherical HDL particles contain a neutral lipid core composed of cholesteryl ester and triglyceride. Thus there is no longer a particle "edge" to constrain the apolipoproteins as in the discs; the surface phospholipid molecules form a continuous monolayer. The apoA-I helices likely float among the phospholipid molecules with their hydrophobic faces penetrating past the phosphate group to interact with the acyl chains (47). With no disc edge, the protein could be envisioned to spread out across the particle surface. Thus, the protein-protein contacts in spheres may be profoundly different from those in the discs. Unfortunately, much less is known about the conformation of apoA-I in spherical particles *versus* discs, even though they make up the vast majority of HDL found in plasma. Segrest *et al.* (48) have suggested that if apoA-I exists in a belt model in discoidal particles, the fundamental interactions of apoA-I helices with the phospholipid acyl chains should not change significantly with the addition of the neutral lipid core. Borhani *et al.* (19) have also argued the similarity in apoA-I structure between the two shapes. These arguments are supported by circular dichroism and fluorescence studies showing that apoA-I secondary structure content and the exposure of Trp residues do not undergo gross changes when a reconstituted discoidal particle converts to a sphere in the presence of lecithin:cholesterol acyl transferase (49).

However, other studies have demonstrated conformational differences in apoA-I on spheres *versus* discs. Careful studies using nuclear magnetic resonance have indicated that the N-terminal portion of the molecule undergoes conformational changes that modify particle charge (50). Furthermore, certain FRET distances measured in spheres are different from those measured in discs (51). An interesting study by Curtiss *et al.* (52) did not directly address conformational differences between discs and spheres but did speak to the effect of changing the composition of the neutral lipid core within spherical particles. The results showed that the core lipid composition could affect specific antibody epitopes within apoA-I. Thus, apoA-I interacts to some extent with the neutral lipid core, opening the possibility that its conformation can change depending on the lipid cargo of a given particle. Unfortunately, the resolution of these techniques was not high enough to distinguish between relatively small adaptations of, for example, a double belt model or a completely different spatial arrangement in the spheres. More experimental distance information is required before we can draw even the most basic relationships between the models determined in the discs to the possibilities within spheres.

Conclusions and Challenges

It can be argued that one of the outstanding questions in vascular biology is how the structure of apoA-I modulates HDL metabolism and function. This highly dynamic molecule is capable of adopting an array of conformations along the RCT pathway. It is the relationship between this *structural* flexibility and the potential for *functional* flexibility that makes understanding apoA-I structure a critical problem. The crystal structures and theoretical models summarized above have provided a solid foundation for understanding apoA-I conformations. As helpful as these have been, a key component in recent advancements has been the clever design of solution-based experiments to independently validate and/or modify these models to reflect physiological situations. As a result, we would argue that the field has a good understanding of at least the generalities of apoA-I organization in its lipid-free form and in simple discoi-

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dal particles. However, it is clear that more work needs to be done to understand the importance of the more dynamic sequences within these structural frameworks. As mentioned above, there is a critical need to derive a similar level of understanding of apoA-I in spherical particles. This may be relatively straightforward for homogeneous reconstituted spheres, but a central challenge will be to extend the studies to the inherently heterogeneous particles obtained from humans. Does apoA-I adopt a double belt organization in authentic human HDL particles? Reconstituted forms of HDL have been under intensive study for nearly 3 decades. Perhaps the time has come to apply that hard-earned knowledge to physiologically relevant particles that exist in the circulation. Given the inherent heterogeneity of human plasma HDL, a major hurdle to these types of experiments will be dealing with the presence of additional proteins including apoA-II. These may not only interact with apoA-I on the HDL surface, but they may also alter its conformation and thus affect the function of a given HDL subclass. These experiments will require a significant departure from traditional spectroscopic techniques that depend on a homogeneous population of particles. Meeting these challenges will be critical if we are to design (and understand the consequences of) therapies to manipulate HDL metabolism.

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