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VASCULAR BIOLOGY (J. HAMILTON, SECTION EDITOR)

Reconstituted Discoidal High-Density Lipoproteins: Bioinspired Nanodiscs with Many Unexpected Applications

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Abstract

Purpose of Review Summarize the initial discovery of discoidal high-density lipoprotein (HDL) in human plasma and review more recent innovations that span the use of reconstituted nanodisc HDL for membrane protein characterization to its use as a drug carrier and a novel therapeutic agent for cardiovascular disease.

Recent Findings Using a wide variety of biophysical techniques, the structure and composition of endogenous discoidal HDL have now largely been solved. This has led to the development of new methods for the in vitro reconstitution of nanodisc HDL, which have proven to have a wide variety of biomedical applications. Nanodisc HDL has been used as a platform for mimicking the plasma membrane for the reconstitution and investigation of the structures of several plasma membrane proteins, such as cytochrome P450s and ABC transporters. Nanodisc HDL has also been designed as drug carriers to transport amphipathic, as well as hydrophobic small molecules, and has potential therapeutic applications for several diseases. Finally, nanodisc HDL itself like native discoidal HDL can mediate cholesterol efflux from cells and are currently being tested in late-stage clinical trials for cardiovascular disease.

Summary The discovery of the characterization of native discoidal HDL has inspired a new field of synthetic nanodisc HDL, which has offered a growing number of unanticipated biomedical applications.

Keywords Nanodiscs · High-density lipoprotein (HDL) · Apolipoprotein A-I · Mimetic peptides · CYP · Drug delivery

Abbreviations

ABC	ATP-binding cassette
LCAT	Lecithin:cholesterol acyl-transferase
apo	Apolipoprotein
DMPC	1,2-Dimyristoyl-sn-glycero-3-phosphocholine
DMPS	1,2-Dimyristoyl-sn-glycero-3-phospho-L-serine
POPC	1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine
DHPC	1,2-Dihexanoyl-sn-glycero-3-phosphocholine
DLPC	1,2-Dilauroyl-sn-glycero-3-phosphocholine
DLPG	1,2-Dilauroyl-sn-glycero-3-phospho-(1′-rac-glycerol)
NBD-PE	(N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl)-1,2-dihexadecanoyl-sn-glycero-3-phosphoethanolamine

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Discovery of Nanodisc HDL

Nanodiscs in human plasma were first reported in 1971 by Trudy Forte when disc-shaped particles were first found in plasma from patients with a genetic defect in lecithin:cholesterol acyltransferase (LCAT), a plasma enzyme that esterifies cholesterol [1]. Transmission electron microsopy (TEM) images contrasted with 2% sodium phosphotangustate revealed a series of discoidal particles stacked in a long rouleau-like formation (Fig. 1). In the same year, this group also reported that dialyzed denatured HDL fractions isolated from normal subjects also contained nanodiscs, with a radius of approximately 100–200 Å and a width of 50–55 Å [2]. Other groups then reported that

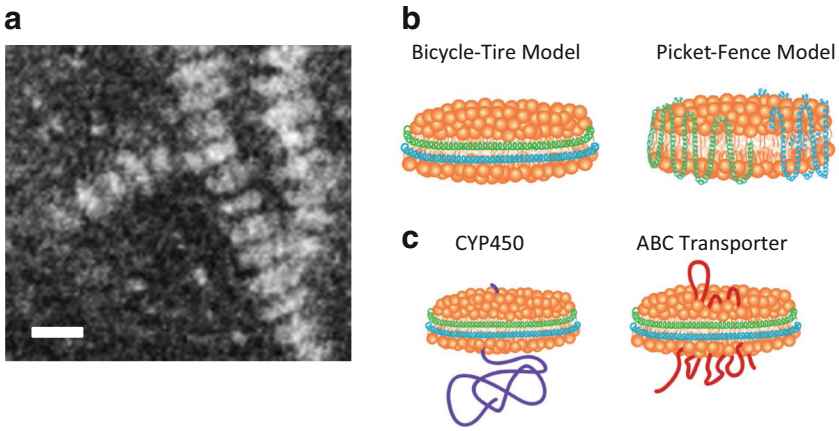

Fig. 1 **a** Electron micrograph of discoidal HDL stacked in rouleau-like formation (the scale bar: 10 nm). **b** Competing models for how apoA-I is wrapped around discoidal HDL. **c** Model for how CYP450s and ABC transporters are reconstituted in nanodisc HDL for structural evaluation

incubation of apolipoproteins isolated from HDL with phospholipids produced disc-like structures similar in size and morphology to those observed in human plasma [3]. Incubation of purified porcine plasma apolipoproteins isolated from HDL with large DMPC multilamellar vesicles was shown to cause the dissolution of the vesicles, which then spontaneously reorganized into HDL-like particles [4]. ApoA-I, the main protein component of HDL, is a tandem array of amphipathic helices and was proposed by Jere Segrest in 1977 to stabilize the disc structure of HDL by wrapping around the side of disc like a "bicycle tire" [5, 6]. This model was later supported by others by the analysis of reconstituted apoA-I and deuterated DMPC or hydrogenated DMPC discoidal particles dissolved in D_2O by a wide variety of physical techniques, such as neutron scattering and electron microscopy [7]. The majority of the protein residues of apoA-I were located at the outer part or edge of the complex in good agreement with the bicycle tire model. Amino acids with hydrophobic side chains were predicted to point inward to the lipid phase of the particles, whereas polar or charged amino acids were arranged in the helix so that they point outward to the aqueous environment. This configuration of amino acids of apoA-I was supported by short apoA-I mimetic peptides that can also bind lipids and form nanodisc HDL [8].

In 1985, a subpopulation of human HDL in plasma that migrated slower than the major fraction of HDL during agarose gel eletrophoresis was found by John Kane's laboratory. The majority of plasma HDL forms spheres with a radius of 90–100 Å and is arranged in micellar-like configuration [9]. The surface lipids are mostly amphipathic phospho lipids, namely phospholipids and free cholesterol, whereas the core contains mostly hydrophobic lipids like cholesteryl ester made by LCAT and a small amount of triglycerides. The slow-migrating fraction of HDL, which was detected with an anti-apoA-I antibody, migrated between HDL and LDL and hence was named pre-β HDL [10] and is strikingly similar to the earlier report by Trudy Forte of discoidal HDL [11]. Others analyzed this HDL subfraction in normolipidemic individuals and found that it represents between 3 and 6% of total HDL [12]. Pre-β HDL is also sometimes called nascent HDL, because it is thought to form when apoA-I, which is secreted by the liver and intestine, extracts phospholipids from cell membranes. When freshly harvested plasma was incubated with skin fibroblasts labeled with [^{3}H]cholesterol for 1 min, [^{3}H]cholesterol first appears in the pre-β HDL fraction when resolved by 2D gel electrophoresis [13]. One-minute incubation with a 2-min chase with non-labeled cholesterol showed that most of the [^{3}H]cholesterol was later transferred into α-migrating HDL, thus spherical forms of HDL.

In 1991, a novel concept was proposed by Shinji Yokoyama in which lipid-free apoA-I interacts with the plasma membrane and assembles pre-β HDL species with cellular phospholipids and cholesterol [14]. This reaction can occur not only with apoA-I but with other exchangeable type apolipoproteins like apoA-II, apoA-IV, apoE, and apolipophorin III, which all contain amphipathic helices [15, 16]. Furthermore, a classical hydrophobic cholesterol-lowering drug, probucol, abolished this apoA-I-mediated cellular lipid efflux and assembly of pre-β HDL [17]. Treating mice with probucol also markedly lowered HDL in plasma, presumably by interfering with this process [18]. In 1999, several groups discovered that ABCA1, a member of the ATP-binding cassette transporter family, was critical in this process by creating lipid domains on the plasma membrane that can be extracted by apolipoproteins [19–22]. It was also discovered to be the defective gene in Tangier disease, which is a rare autosomal recessive disorder of low HDL and the accumulation of excess intracellular lipids, particularly in macrophages [23, 24]. Altogether, these discoveries fit nicely with the long proposed hypothesis that HDL is anti-atherogenic because it promotes the removal of excess cellular cholesterol from cells and then eventually returns it to the liver for excretion by a pathway called reverse cholesterol transport [25].

Recent Structural Studies of Nanodisc HDL

The initial structural model for apoA-I on a unilamelar bilayer discoidal particle (DMPC:DMPS, 9:1) was later modified by an upgraded polarized internal reflection infrared spectroscopy which indicated a parallel double-belt configuration sometimes called the bicycle tire model (Fig. 1) [26]. A competing model at the time was the picket fence model in which the individual helices were oriented so that they were parallel to the acyl chains in a picket fence–like configuration (Fig. 1) [27]. Subsequently, other researchers described a more detailed molecular belt model of the smallest discoidal HDL particle containing 160 lipid molecules, surrounded by two apoA-I molecules in antiparallel formation. The 11 amino acid residues per 3 turns model, 11/3 model, of the amphipathic helix seems to best fit with a predicted curved apoA-I of 105 Å in diameter in outer surface of the nanodisc and with 85 Å diameter of the inner side facing to the lipid bilayer [28]. The structure of apoA-I on reconstituted particles was also evaluated by cross-linking and also supports the antiparallel double-belt model [29, 30]. By using a N-terminal truncated variant of apoA-I, two strands of apolipoprotein A-I were found to wrap around the circumference of the disc in an "antiparallel, belt-like fashion" as first described in the bicycle tire model [31]. An alternative structure of apoA-I on the pre-β HDL was then introduced in 2007 [32], called the solar flare model. In this model, the N-terminal globular domains were proposed to protrude out from the lipid rim and interact with LCAT [33, 34]. The precise detailed LCAT-binding epitope of the antiparallel apoA-I dimers on nanodisc HDL has recently reported [35], including the helix5/helix5 registry of the two helices of apoA-I that are optimum for LCAT activation.

Nanodisc HDL for Structural Studies of Membrane Proteins

Lipid nanodiscs are discoidal bilayer particles stabilized by a membrane scaffold protein [36–38]. The use of lipid nanodiscs for structural studies of membrane proteins is now widely used, due to their many advantages over the classical platforms used for this purpose, such as liposome reconstitution and detergent micelles. The isolation and analyses of membrane-bound proteins or integral membrane proteins typically require the use of detergents, but the native configuration of proteins in the lipid bilayer and their functionality may not be accurately captured by this procedure. Nancodisc HDL has, therefore, been explored as a novel tool to reconstitute membrane proteins in their native form.

An early example of this approach used purified human apoA-I [39] as nanodisc scaffold protein for investigating the structure of cytochrome P450 proteins [40]. Because these membrane proteins typically contain a single hydrophobic membrane-anchoring domain, it is difficult to generate crystals suitable for analysis by X-ray diffraction. It was possible, however, to obtain some structural information on CYP2B4 by the atomic force microscopy when it was reconstituted in a phospholipid bilayer of nanodisc HDL (Fig. 1) [40]. When reconstituted in this nanodisc HDL, CYP2B4 was found to project approximately 3.5 nm higher than its lipid-water boundary. The complex was also shown to be functional in regard to the electron transfer by its interaction with a specific reductase [41–43]. Subsequent to these early efforts to use nanodisc HDL containing apoA-I, specific proteins to stabilize the disc called membrane scaffold proteins (MSP) have been developed [44]. In many cases, membrane protein nanodisc complexes can be investigated using methods already established for detergent solubilized membrane proteins. For example, the N-terminal globular domain of apoA-I was truncated and replaced with a His-tag and TEV protease recognition sequence that can later be cleaved off with TEV protease after the purification. Dimers of these MSP were shown to self-assemble with cholate-suspended DPPC into a nanodisc after a simple dialysis process [44]. Briefly, target membrane proteins of interest were solubilized with Emulgen 913 and cholate and were mixed with membrane lipids and the MSP. Detergents used in this process can be removed by dialysis and incubation with Bio-Beads. This method was first applied for CYP3A4 and its structure was detected in a MSP nanodisc by small-angle X-ray scattering (SAXS). Furthermore, it was found to be functional as revealed by its high-affinity binding of testosterone and its ability to hydroxylate this substrate [45]. These MSP have been designed to form nanodiscs with diameters between 6 and 8 nm, offering superior spectral acquisition performance in solution-state NMR [46], while still allowing for protein-lipid interactions that may play a key role in the correct folding and function of the membrane protein under study [47].

In another example, human CYP17A1 was incorporated into the nanodiscs and the function of active site residue, Thr306, in its activity was investigated [48]. Several plant CYPs, such as CYP79A1, and CYP71E1, and their corresponding CYP reductases, have also been incorporated into nanodiscs for functional studies [49]. In this case, the membrane scaffold protein MSP1E3D1 was used along with DLPC, DLPG, and NBD-PE [49]. MSP1E3D1 differs from the original MSP by additional of a 3 helices (22-mer amphipathic helix) insertion between helix4 and helix5, which allows the formation of nanodiscs as large as 12.9 nm in diameter for the analysis of larger membrane proteins [50]. In contrast, MSP1D1ΔH4ΔH5, which lacks helix 4 and helix 5, can be used to generate much smaller nanodisc of 4 nm in diameter [51].

The structure of the ABC transporters, ABCB1 (MDR1, Pgp) and MsbA, the bacterial homolog of ABCB1, have also been examined using nanodiscs made with MSP1E3D1 [52,

53]. In this case, these proteins have multiple transmembrane domains that span the nanodisc structure (Fig. 1). Interestingly, three independent groups reported the basal ATPase activity of MsbA in nanodiscs to be at least 7-fold greater compared to detergent solubilized protein [52, 54, 55], while maintaining similar Km, indicating that the nanodisc reconstitution did not adversely affect substrate binding [52]. Furthermore, Zoghbi et al. [52] used luminescence resonance energy transfer decay (LRETD) to investigate the spatial separation of the catalytic nucleotide-binding domains (NBDs). Under the near physiological conditions afforded by nanodiscs, the NBDs exhibited two predominant conformational states with short separations of 36 Å and 47 Å between labeled Cys561 in each of the dimer forming NBDs. Detergent-solubilized MsbA, on the other hand, showed a single near exclusive separation of 53 Å between the NBDs. By comparison, the structure of *V. cholera* MsbA, crystallized in the presence of the non-hydrolyzable ATP analogue AMP-PNP, reveals an inward closed nucleotide bound state, with a separation of ~ 36 Å between the corresponding residues. This observation is in line with LRETD performed on nanodisc reconstituted and detergent solubilized MsbA, during the hydrolytic cycle, which in both cases leads to a marked shift to the 36 Å distance state. The close proximity of NBDs in the nanodiscs is the likely reason for the higher basal ATPase rate, since the catalytic cycle requires smaller conformational changes to bind, hydrolyze, and release the ATP substrate, as compared to the detergent-solubilized form [52]. Nanodiscs have been successfully generated from both defined mixtures of purified lipids, such as POPC, POPS, and cholesterol, as well as whole tissue lipid extracts [56]. This constitutional flexibility makes them particularly attractive since membrane proteins have evolved to function in the defined lipid composition of their host organism and cell type, which produce a characteristic micro-environment that detergents cannot accurately mimic. Therefore, nanodiscs can be tailored to probe the effect of specific lipids on protein function [56], without detrimental interference from detergents [57].

Short synthetic peptide mimetics of apoA-I have also been used to generate nanodisc HDL for structural studies on what was called bicelle-embeded membrane proteins. One such peptide called 22A (PVLDLFRELLNELLEALKQKLK) [58] was used to obtain the NMR structure of CYP2B4 [59–63]. By using a mixture of long-chain phospholipids, DMPC, and short-chain phospholipid/detergent, DHPC [59–63], the diameter of nanodiscs was found to depend upon the lipid:peptide ratio. Nanodiscs made with 22A peptides containing both CYP2B4 and CYTB5(cytb5) were stable for at least 10 days after preparation. Structural analysis by NMR was consistent with previous reports and newly identified Leu75 as a critical amino acid residue involved in the binding interface between CYP2B4 and CYTB5. The authors concluded that the conformation and catalytic activities observed in nanodiscs better reflect the in vivo state of CYPs and MsbA and highlight the importance of lipid environment in the study of membrane proteins which rectify the integral anchored domain, transmembrane domain, and juxtamembrane domains of proteins.

Nanodisc HDL for Drug Delivery

Nanodisc HDL has also been exploited as drug delivery vehicles with amphipathic drugs carried on the surface of the particles, whereas more hydrophobic drugs get buried in the acyl chains of the phospholipids, which converts discoidal HDL into a more spherical form with the drug in the hydrophobic core of the particle. Counsell et al. [64] were the first scientists to propose the potentially favorable characteristics of lipoproteins as drug delivery, but HDL was not tested for this purpose until many years later by Schouten et al. [65] in 1993. Today, the idea of using nanodisc HDL as drug delivery vehicles is a rapidly growing field, because HDL possesses a number of advantageous features that makes it an almost perfect transporter of diagnostics and therapeutic agents [66, 67]. These include its biocompatibility, payload capacity, long circulating half-life, and selective targeting and controlled release capability [67]. As already discussed, HDL can be easily reconstituted in vitro from its major surface components apoA-I and phospholipids [68], and during this procedure, a drug of interest can be added and is readily incorporated into HDL, particularly if it is amphipathic or hydrophobic. Structural and compositional features of reconstituted forms of HDL, nanodisc HDL, are also highly and easily customizable [69]. Moreover, besides their capacity to deliver drugs, HDL has also been used to deliver imaging agents and hence the term theranostics has been often used to describe this field [70].

Some early examples of the use of discoidal nanodisc HDL as drug carriers include poorly water-soluble drugs, like the antifungal compound amphotericin B [71] and the strongly neurotoxic all-trans-retinoic acid [72]. Integration of amphotericin B into nanodisc HDL effectively solubilized this antibiotic, which was found to have potent in vitro and in vivo antifungal activity, with no observed toxicity at therapeutic doses [71]. The use of nanodisc HDL for integration of all-trans-retinoic acid showed that nanodisc HDL is a useful vehicle for solubilization and delivery of drug to hepatoma cell lines [72]. Nanodisc HDL has also been utilized as delivery agent to improve low-bioavailability drugs for cancer [73–76] and Alzheimer's disease [77, 78]. Formulation of nanodisc HDL with curcumin was successfully used in targeting hepatoma, mantle cell lymphoma, and glioblastoma multiforme cell lines [73–75]. The use of monocholesterylsuccinate (CHS)-modified paclitaxel-loaded nanodisc HDL prevented its premature release and improved its efficacy in tumor-bearing mice [76]. It has been

recently shown that nanoparticles made from apoE3 and nanodisc HDL (apoE3-rHDL, ANC: ApoE reconstituted HDL nanocarrier) decreased amyloid β deposition, attenuated microgliosis, ameliorated neurologic changes, and rescued memory deficits in a mouse model for Alzheimer's disease, the senescence-accelerated mouse-prone 8 (SAMP8) mice [77]. Similar results obtained from SAMP8 mice treated with apoE-rHDL nanodisc loaded with a polyphenolic agent, α-mangostin, showed that these nanodiscs possess both amyloid β-targeting ability and blood-brain barrier permeability [78]. Moreover, studies on use of radiolabeled nanodisc HDL for quantitative positron-emission tomography imaging of tumor-associated macrophages in a breast cancer model showed its potential for non-invasive imaging, and in this same study, HDL was used to simultaneously deliver nucleic acids for altering gene expression in target cells [79].

The use of HDL as a drug carrier has come a long way since the original proposal of Schouten et al. [65], but so far it has only been tested in animal models and much more work still needs to be done in this area.

Nanodisc HDL for Cardiovascular Disease

Perhaps it is only fitting that nanodisc HDL has also been harnessed for the likely physiologic role of HDL, the removal of excess cellular cholesterol. A wide variety of different HDL preparations made with full-length apoA-I protein or short apoA-I mimetic peptides have been shown to reduce atherosclerosis in animal models and have also been tested in early-stage clinical trials for the treatment of cardiovascular disease [80].

This work was inspired by the pioneering studies by Jere Segrest and G. M. Anantharamiah, who using synthetic peptides, first described the structural motifs necessary for lipid binding by apolipoproteins [8]. Nanodisc HDL particles made with either apoA-I or synthetic peptides were later shown to remove cholesterol and phospholipid from cells in an ABCA1-dependent mechanism [81, 82]. Similar to the situation with anti-microbial peptides [83], apoA-I mimetic peptides with too high a hydrophobic moment are potentially cytotoxic, most likely because of their ability to extract lipid in a non-ABCA1-dependent pathway [81]. Efforts have, therefore, been made to improve the specificity of these peptides for only removing cholesterol by ABCA1 [84–86]. As described in the structure study for membrane protein, nanodisc HDL with 22A apoA-I mimetic peptide (22A-HDL) was also applied for delivery of macrophage liver X receptor (LXR) agonist. The treatment with drug carried 22A-HDL successfully increased LXR target proteins of hepatocytes and macrophages in apoE-null mice [87].

Several early-stage clinical trials, involving the intravenous infusion of nanodisc HDL made with full-length apoA-I either purified from plasma or recombinantly produced, have now been completed [88–107]. The treatment appeared to be safe and after only a few treatments appeared to markedly reduce plaque size [92, 97], as assessed by intravascular ultrasound, but some subsequent larger studies have failed to show a benefit [91]. A large phase 3 clinical trial treating the patients with cardiovascular disease with nanodisc HDL made with apoA-I purified from plasma is currently underway [101, 107]. Nanodisc HDL made with synthetic peptides has also been shown to be safe in early-stage clinical trials and peptides made with D-amino acids have also been tested as oral agents [108–110] but considerable more work needs to be done in this area. Finally, the extracorporal transformation of spherical HDL from plasma into nanodiscs by a plasmapheresis type device has been described [111]. Nanodisc HDL produced in this way is potent in effluxing cholesterol from cells and can be reinfused back into patients and is being tested in early-stage clinical trials [112].

Future Prospective

It has been a long and winding road from the first discovery of nanodisc HDL to its detailed structural analysis and now it has many structural biology and biomedical applications. Further improvements in the design of the apoA-I mimetic peptides and the inclusion of different types of lipids may further enhance the utility of nanodisc HDL. Alternatively, short amphiphilic polymers, such as styrene-maleic acid copolymer, can be a substitute for apoA-I or mimetic peptides for reconstituting membrane proteins in nanodisc HDL-like structures [113]. Related polymers made with polystyrene called amphipols have recently shown promise for structural studies of membrane proteins and potentially can possibly be used as an alternative scaffold for nanodisc HDL [114]. Besides cardiovascular disease, reconstituted nanodisc HDL has surprisingly potent anti-inflammatory effects and has been shown in animal models to have possible value in a wide variety of infectious and inflammatory diseases. A new frontier for nanodisc HDL is exploring its possible therapeutic use in a variety of neurodegenerative diseases like Alzheimer's disease [115]. Progress in these many areas, however, will likely require a better understanding how the protein and lipid composition of HDL relates to its many biological functions, which likely inform us in how to best prepare and use nanodisc HDL particles in the future.

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Compliance with Ethical Standards

Conflict of Interest Maki Tsujita, and Daniel A.P. Gutmann declare no conflict of interest. Alan Remaley and Anna Wolska are co-inventors on several patents related to the therapeutic use of apolipoprotein mimetic peptides.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the any of the authors.

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