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Why Targeting HDL Should Work as a Therapeutic Tool, but Hasn't

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Abstract

Atherosclerosis is one of the most common causes of death and disability in US today despite the availability of statins which reduce hyperlipidemia, a risk factor that predisposes individuals to this disease. Epidemiology of human populations has overwhelmingly demonstrated an inverse correlation between the concentration of plasma HDL cholesterol (HDL-C) and the likelihood of developing cardiovascular disease (CVD). Decades of observations and mechanistic studies suggest that one protective function of HDL is its central role in reverse cholesterol transport (RCT). In this pathway the ATP-binding cassette transporter (ABCA1) releases intracellular cholesterol, which is packaged by apolipoprotein A-I (apoA-I) into nascent HDL (nHDL) particles and released from the plasma membrane. Further lipidation and maturation of HDL occurs in plasma with the eventual uptake by the liver where cholesterol is removed. It is generally accepted that CVD risk can be reduced if plasma HDL-C levels are elevated. Several different pharmacological approaches have been tried, the most popular approach targets the movement of cholesteryl ester from HDL to triglyceride rich particles by cholesteryl ester transfer protein (CETP). Inhibition of CETP increases plasma HDL-C concentration, however, beneficial effects have yet to be demonstrated, likely the result of off-target effects. These revelations have led to a reevaluation of how elevating HDL concentration could decrease risk. A recent, landmark study showed that the inherent cholesterol efflux capacity of an individual's plasma was a better predictor of CVD status than overall HDL-C concentration. Even more provocative are recent studies showing that apoA-I, the principle protein component of HDL, functions as a modulator of cellular inflammation and oxidation. The following will review all of these potential routes explaining how HDL apoA-I can reduce the risk of CVD.

Keywords

apolipoprotein A-I; high density lipoprotein; atherosclerosis; lipid raft; inflammation; nascent HDL; cholesterol transport; cardiovascular disease; cholesterol efflux

HDL Cholesterol and Predicting Cardiovascular Risk

Atherosclerosis is responsible for over half of the yearly mortality in the US, with more than 500,000 people dying of this disease annually. Human population studies along with cause and effect experiments with animal models have shown an inverse correlation between the

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concentration of plasma HDL-C and the risk of developing atherosclerotic cardiovascular disease (CVD) (1–5). ApoA-I carried by HDL plays a central role in a process called reverse cholesterol transport (RCT), which describes the transfer of peripheral tissue cholesterol by HDL to the liver for excretion (6–8). From studies it appears that the ATP-binding cassette transporter A1 (ABCA1) in extra hepatic cells lipidate apoA-I with glycerophospholipid and cholesterol to form stable nascent HDL[1] particles of defined size and composition, regardless of the cell type. Once released into plasma, lecithin:cholesterol acyltransferase (LCAT) converts nHDL cholesterol to cholesteryl ester (CE) resulting in a spherical lipid-rich HDL having a core of CE. Additional lipidation of HDL can take place with ATP-binding cassette transporter G1 (ABCG1) which has been reported to lipidate mature, spherical HDL (9), while the scavenger receptor class B1 (SR-B1) removes CE from mature HDL for catabolism and excretion by the liver (10, 11).

Because of a wealth of epidemiological evidence, drug discovery has focused on ways to increase plasma HDL-C concentrations with the hope of ultimately decreasing arterial cholesterol retention, immune cell infiltration and cardiovascular events. Lifestyle changes, like smoking cessation, exercise, etc., may modestly increase HDL-C levels 5–10% and have been met with limited success. Pharmacologic approaches include treatment with niacin or with cholesteryl ester transfer protein (CETP) inhibitors. A trial of over 3400 total patients that administered niacin and simvastatin increased HDL-C levels about 20%, but showed no incremental clinical benefit of niacin to the simvastatin therapy when compared to the control population receiving simvastatin plus placebo (12). A study of the CETP inhibitor, torcetrapib, reported a 72% increase in plasma HDL-C concentration, but was halted due to an increased risk of mortality and morbidity due adverse effects of unknown etiology (13). Studies with the CETP inhibitors evacetrapib, dalcetrapib and anacetrapib, all of which substantially increase plasma HDL-C levels, are on going, and have yet to show a reduction in cardiovascular events (14–16). What confounds the HDL RCT hypothesis further, is that a speedy improvement in health status did not follow the dramatic increases in plasma HDL-C concentration.

HDL-C is a measure of plasma HDL-associated cholesterol, but does not give information on the number of HDL particles, HDL size distribution or free versus ester cholesterol composition, factors which may be important to the role of HDL. If higher plasma HDL-C concentrations are not immediately protective against CVD then what feature of the HDL particle might be protective at the level of the individual? As a possible answer to this question recent studies have suggested that the cholesterol efflux capacity of an individual's plasma is a better predictor of CVD status than HDL-C cholesterol concentration alone (17). When HDL does not appear protective it might be classified as dysfunctional, a term associated with HDL particles that have been modified and thus, are no longer protective (18, 19). Because apoA-I is the principal protein component of HDL, its role in cholesterol metabolism and inflammation are under active investigation (20). Complementing its role in RCT, apoA-I in combination with ABCA1 may also inhibit cellular inflammation (21–35) suggesting that inflammatory mechanisms contribute to the development of atherosclerosis (36–38). We will address why the HDL-related reduction in CVD risk is not exclusively

[1] The term nascent HDL (nHD) is sometime misunderstood and should be distinguished from plasma HDL that is steady state lipoprotein particle modified by numerous enzymes and proteins and often quantified by its cholesterol concentration, HDL-C. Nascent HDL should be distinguished from recombinant HDL (rHDL) which is a synthetic HDL particle prepared *in vitro* by removing sodium cholate from synthetic phospholipid mixed micelles in the presence of lipid free apoA-I. Instead, nHDL are generated by the action of ABCA1 on apoA-I. One reason for this distinction is the common assumption that nHDL, like rHDL, can only package about 10% of its total lipid as free-cholesterol in a phospholipid bilayer possessing a discoidal shape. Recent studies using mass spectrometry showed that a lipid-rich nHDL particle produced by ABCA1 was spheroidal and contained most if not all the free cholesterol necessary for the LCAT mediated conversion to a mature cholesteryl ester rich HDL (51).

dependent on the plasma concentration of HDL-C or apoA-I and propose additional mechanisms that might explain apoA-I's anti-atherogenic properties.

HDL, Inflammation and Atherosclerosis

Atherosclerosis has been described as a chronic inflammatory state characterized by the accumulation of cholesterol and immune cells within the artery wall. Early reports for humans and animal models suggest that individuals who consume a cholesterol-rich diet rich will have higher plasma cholesterol levels. As a result of increased plasma cholesterol, low density lipoprotein (LDL) concentrations are elevated. Regions in the artery wall where net influx exceeds efflux accumulate cholesterol resulting in lipid deposition. Inflammation appears to be a cause or consequence of fat deposition in a process that probably involves the secretion of chemokines and modulation of inflammation (39–45) a target for reducing atherosclerosis.

In a mouse model that lacks both apoA-I HDL and LDL receptor (LDLr) (LDLr$^{-/-}$, apoA-I$^{-/-}$) feeding an atherogenic diet induces the expansion of T, B and dendritic cells that become CE-enriched, which can be completely reversed by treatment with lipid-free apoA-I (46, 47). If not treated the chronic expansion of immune cells in LDLr$^{-/-}$, apoA-I$^{-/-}$ mice leads to an autoimmune-like phenotype, characterized by skin lesions and panniculitis (48, 49) and death (27, 50). Resolution of panniculitis occurred following subcutaneous administration of small amounts of lipid-free apoA-I, a process that was associated with an increase in the Treg to Teff cell ratio (47). Interestingly, resolution of this phenotype was independent of significant changes in plasma HDL cholesterol concentrations (~4 mg/dL). Activation of endothelial cells or smooth muscle cells has been shown to initiate an inflammatory response characterized by the release of chemokines and adhesion molecules that direct monocytes to the affected region of the vessel wall (44, 51–53). Atherosclerosis seems to be driven by the influx of monocytes that differentiate into inflammatory cells once within the artery wall (41). Resolution of atherosclerosis would then, it seems, require reduced recruitment of monocytes, reduced activation of these monocytes and removal of lipid-laden inflammatory cells already resident in the vessel wall. Potteaux et al. (38) using an apoE-deficient mouse model have concluded that suppressed monocyte recruitment was an essential feature of disease regression. In this model there were fewer activated, circulating monocytes and reduced expression of adhesion receptors. Now it would be anticipated that if inflammatory cells have accumulated cholesterol then the egress of these cells and/or their ability to off-load cholesterol becomes a limiting step for the removal of cholesterol from the vessel wall. Potteaux et al. (38) suggest that the lipid-laden inflammatory cells do not egress from the artery wall, but undergo apoptosis. Therefore, the clean up step(s) to remove lipid would most likely involve phagocytosis of dysfunctional, lipid-laden macrophages and expulsion of excess lipids by ABCA1 to apoA-I (54). Over-expression of apoA-I in macrophages has been suggested to delay the progression of atherosclerosis by stimulating ABC-dependent cholesterol efflux in apolipoprotein E-deficient mice (55).

Cholesterol Efflux Capacity and nHDL Biogenesis

Efflux capacity appears to be driven by the presence of a lipid-poor HDL subfraction, termed preβ-1 HDL (56), named for its unique 2-D agarose electrophoretic migration. The involvement of this lipid-poor monomeric apoA-I containing particle is of interest because they are either rapidly converted to larger lipid-rich, mature HDL by LCAT or removed by the kidney. Once formed, preβ-1 HDL do not appear to undergo further lipidation by ABCA1 (57, 58). Because efflux studies have shown that preβ-1 HDL is the principal acceptor of cholesterol and the driving force behind efflux capacity (17), it may be possible

that these particles are remodeled at the cell surface, releasing lipid-poor apoA-I that can then be re-lipidated by ABCA1. Remodeling of mature lipid-rich HDL at the cell membrane surfaces, possibly through SR-B1 (59), has been shown to contribute to the formation of preβ-1 HDL, and thus, increase the overall cholesterol efflux capacity (60). However, preβ-1 HDL is only one of several nHDL particles formed by the interaction of apoA-I with ABCA1 (61, 62). Recent studies using mass spectrometry show that a lipid-rich nHDL particle produced by ABCA1 is spheroidal and contains most if not all the free cholesterol necessary for the LCAT mediated conversion to a mature CE rich HDL (61). Enhanced generation of the largest particle by ABCA1, a 10–12 nm diameter nHDL containing 108 molecules of free cholesterol and 130 phospholipids solubilized by 3 molecules of apoA-I, would be the most productive particle for mobilizing cellular cholesterol from the periphery. In many respects, this larger particle has a lipid composition similar to that of apoA-I containing particles isolated from LCAT-deficient patients (63, 64), but different from mature HDL subfractions (65). A comprehensive study of ABCA1 generated nHDL particle composition (61, 62) uncovered a striking similarity between the sphingomyelin and cholesterol content of 10–12 nm nHDL and the composition of lipid rafts (66, 67). More accurate methods of quantifying HDL and its various subfractions will improve our understanding of how apoA-I conformation and lipid composition influence anti-atherogenic properties of HDL (68).

As lipid rafts are essential for regulating signaling and activation of immune cell G protein–coupled receptors (69–71), there is an obvious association between apoA-I's anti-inflammatory function and the control of innate and adaptive immune cell activation status (53). Therefore, the lipid link between monocyte and T cell receptor function and atherosclerosis (31, 38, 72–74) suggests that apoA-I should have a systemic anti-inflammatory effect that will hinder disease progression. Despite uncertainties surrounding the mechanism explaining HDL/apoA-I mediated protection against cardiovascular disease, there are many published examples of the efficacy of infusing recombinant HDL into animal models of atherosclerosis (44, 59, 75, 76) and in humans (77–84).

Raising Plasma HDL-C Protects Against CVD: Transport of Cholesterol

The most accepted theory explaining the protective features of HDL apoA-I is based on the idea alluded to earlier with its role in RCT (85–87). ABCA1 transports cholesterol and phospholipids out of cells to apoA-I and assists in the formation of nHDL (61, 62). Since the liver is one of the major producers of apoA-I as well as the main site of cholesterol excretion, this pathway is exceptionally important for maintaining bulk plasma HDL-C levels (88). Much of the CE accumulated by HDL is derived from LCAT-catalyzed maturation of nHDL into spherical, mature HDL that is somewhat larger than the starting nHDL (89, 90). Nascent HDL carries no CE, but considerably more free cholesterol compared to mature HDL (61). The source of additional lipids added to HDL is most likely from the remodeling of plasma low density lipoproteins (LDL) by CETP and phospholipid transfer protein (PLTP). At the liver, SR-B1 binds mature HDL and removes cholesterol for catabolism and excretion (10, 11). However, the anti-atherogenic aspect of this pathway suggests that plasma HDL is responsible for transporting excess cholesterol mass from extra-hepatic sources, e.g., the arterial wall, back to the liver for removal. To accomplish this transport, as alluded to earlier, HDL must be remodeled at peripheral sites to release lipid-poor apoA-I if ABCA1 is to participate in the RCT process by generating new HDL particles that would be transported by the plasma. There is, however, some evidence in animal models that the overall rates of RCT are not affected by increasing HDL-C levels or up regulating individual steps in the RCT pathway and that the rate of RCT is at maximum velocity for normal levels of HDL-C (91–94). However, infusion of a smaller apoA-I containing, lipidated particles, recombinant HDL (rHDL), into mice was found to increase

cholesterol efflux from tissues to plasma (94) and over-expression of apoA-I was found to favor efflux of cholesterol from lipid-laden J774 cells injected into mice that had been treated with apoA-I adenovirus (95). The route of cholesterol transport may also play an important role in RCT. Lymphatic vessels have also been shown to support cholesterol transport from various tissues including the aortic wall. These studies suggest that lymphatic transport may facilitate cholesterol clearance and may be a future target of therapies that reverse atherosclerosis (96).

Raising Dysfunctional HDL Contributes to CVD: HDL and its Cargo

A second hypothesis explaining the anti-atherogenic effect of HDL is based on the cargo that plasma HDL particles carry in plasma (97–100). Depending on the types and amounts of its cargo HDL can become dysfunctional, a term associated with HDL that has lost its anti-inflammatory properties and correlated with ineffective RCT (101). Some of the many protein molecules that bind to HDL include antioxidant enzymes which maintain particle integrity and functionality (102–107) like platelet-activating factor acetylhydrolase (108), while other cargo may directly influence the inflammatory status of cells with which plasma HDL particles interact (105, 109). Recently discovered microRNAs (miRNA) are carried by HDL and delivered to cells through SR-B1 with the possibility of gene regulatory consequences (110). For example, over expression of miR-33, an miRNA encoded by an intron of the gene for SREBP-2, has been shown to reduce the concentration of HDL-C through its suppression of sterol transporters and cholesterol homeostasis (111, 112).

The lipid cargo may include a variety of oxidized lipids generated by reactive oxygen species that are transported to the liver for catabolism (113, 114). Some of the products of the oxidation process produced agents (76, 115, 116) that modify the protein component of HDL with the possibility of generating dysfunctional HDL. Other cargo are molecules that function as lipid mediators which moderate cell and tissue function. Sphingosine 1-phosphate (S1P) is an important lipid mediator for vascular and immune systems that is carried by HDL (117, 118) (119–121) through association of HDL with apolipoprotein M (apoM) (122, 123). The reports suggest that about 1 to 10% of HDL particles carry S1P with only about half of the apoM carrying S1P. A report by Kontush et al. has suggested that S1P is asymmetrically distributed among HDL subfractions with the highest levels on smaller, more dense HDL (65). The nature of the association between S1P and apoM was revealed by the discovery of an S1P binding pocket on apoM (122). Arkensteijn et al. have reviewed the literature on apoM and the immunomodulator FTY720, a synthetic S1P analogue agonist for S1P receptors 1,3,4 and 5 (124, 125), in several transgenic mouse models (126). The general trend suggested by the review is that atherosclerosis is inhibited with the loss of apoM or treatment with certain concentrations of FTY720. Studies in humans have now established that concentrations of plasma HDL/apoM S1P are predictive of heart disease risk (123, 127–130).

Sphingosine-1-phosphate regulates vascular permeability and modulates lymphocyte egress from lymphoid tissues (131, 132). Both pro- and anti-atherogenic effects have been attributed to S1P, hinting that it plays a more complex role in the initiation and progression of atherosclerosis (130, 133–136). Some of the complexity is likely due to the tightly regulated synthesis and degradation of S1P by diverse cell types and through its interaction with five different S1P receptors (S1PR 1–5) on cellular membranes (137). S1P can be synthesized by many cell types and serves as an essential signal for both innate and adaptive immune responses (138). Since atherosclerosis has been described as a chronic, inflammatory disorder characterized by the up regulation of a myriad of chemokines and their receptors (40, 73, 139, 140) discerning the role of HDL associated S1P on the global cytokine network would be highly beneficial (138). Interestingly, FTY720 is now an FDA

approved treatment for human patients with multiple sclerosis (132). The phosphorylated form of FTY720 suppresses immune responses by preventing the recruitment of immune cells into inflamed tissue and has been shown to be effective in reducing immune cell recruitment into atherosclerotic lesions in some, but not all, mouse models of atherosclerosis (141–144). Differences in FTY720 efficacy in preventing the development of atherosclerosis may be a consequence of variations in the dose administered, the specific mouse models that were studied, and/or the route of administration.

Effects of ApoA-I on Lipid Membrane Raft Integrity: G-Protein Coupled Receptors, Cytokine-Chemokine Activation

A third suggestion that could explain apoA-I's anti-atherogenic role relates to its connection to the maintenance of lipid rafts on the plasma membrane (71, 145–148). Consistent with this speculation a recent report by Zhu et al. has shown an increase in lipid raft content in macrophage membrane from a macrophage specific ABCA1 knockout mouse model (149, 150). This process does not involve the redistribution of large quantities of cholesterol, but in fine tuning of the lipid raft content of the plasma membrane. Many inflammatory processes are mediated through G-protein coupled receptors that re-locate to specialized regions of the plasma membrane, lipid rafts, that have unique lipid compositions (69, 71, 151), after they are activated. For example, receptors for chemokines are reported to show lipid raft-colocalization (152–154) and Zukovsky et al. suggest that cholesterol binding sites in CXCR4 and CCR5 are responsible for the presence of these receptors in rafts (155). Chemokine receptors, particularly CCR5 have been associated with the progression of atherosclerotic plaques (42). Another important signaling molecule, S1P discussed above, has its G-protein coupled receptors (117) associated with lipid rafts called caveolin enriched microdomains (156). Recent reports have shown that the total lipid composition of nHDL from ABCA1-expressing cells are almost identical to the composition of lipid rafts from the same cells from which the nHDL was derived (61). These results suggest that the fraction of lipid raft on the plasma membrane would be less when ABCA1 was actively loading lipid onto apoA-I.

To carry out lipid-raft remodeling the ABCA1-facilitated transport of cholesterol requires lipid-poor apoA-I, but as pointed out earlier, the plasma concentration of lipid-poor apoA-I is very low. Most apoA-I is synthesized, lipidated and then released into plasma by the liver and intestine. To accommodate the need for lipid-poor apoA-I HDL must be a processed *in situ* to regenerate lipid-poor apoA-I for use as an acceptor. Previous studies have shown that there is a decrease in HDL size associated with HDL modification by CETP, hepatic lipase and other lipoproteins (157, 158). Despite their low concentrations, studies have suggested that preβ-1 HDL or lipid-poor HDL is the principal entity driving efflux capacity. Based on this observation it seems reasonable to assume that mature HDL maybe remodeled, releasing lipid-free or lipid-poor apoA-I at the cell surface that is subsequently lipidated by ABCA1. Likewise, SR-B1 may also be involved in a process that remodels mature lipid-rich HDL at the cell membrane surfaces (59, 60) releasing apoA-I to be reutilized for nascent HDL synthesis.

Conclusion

Because of the well established inverse relationship between plasma HDL-C level and CVD in humans, the emphasis for drug-discovery has been on using HDL-C levels to assess individual patient risk and drug efficacy. The reason this approach has not succeeded is likely related to the complexity of biochemical pathways which regulate steady state plasma HDL-C concentrations in humans. HDL-C is generally predictive of CVD risk and it follows that the analysis of pathways contributing to HDL-C should lead to a specific mechanism

through which HDL, or apoA-I, maintains lower levels of cholesterol in the artery wall. Because increasing HDL-C does not universally reduce CVD risk suggests that in some individuals one or more specific pathways are not functioning properly. As we have refined our understanding of *how* HDL apoA-I protects against CVD it is necessary to go beyond the HDL-C measurement to develop not only more precise indicators (8, 159), but a panel of indicators that score overall HDL function in the individual.

Our particular bias is that the key pathway(s) that reduces cholesterol deposition in the artery involves the participation of apoA-I as a mediator of immune cell activation or status. This mechanism relies on the ability of apoA-I to endothelial and inflammatory cell signaling to diminish the influx of monocytes and other inflammatory cells into the vessel wall. Because many monocytes express both scavenger receptors and the LDL receptor they accumulate LDL in an environment where it is often modified or oxidized. These cells often become damaged and undergo apoptosis, but the numbers of monocytes are maintained by continuous resupply from the vascular pool. Implementing interventions that reduce recruitment of monocytes to the artery wall and increase the concentration of lipid-poor apoA-I will no doubt dramatically reduce the morbidity of CVD in the general population.

In summary, reverse cholesterol transport is the pathway the moves cholesterol among compartments through the plasma to the liver for excretion. This process includes the removal of cholesterol from the artery wall. However, cholesterol derived from the artery wall contributes only a small amount to the bulk of plasma HDL-C transported and is thus difficult to assess. Given the number and complexity of biochemical pathways contributing to plasma HDL-C concentration, continued use of this single measure as a means of assessing risk or efficacy seems outdated and misleading. Although reverse cholesterol transport is an important process, quantitative descriptors of endothelial and immune cell cholesterol maintenance are necessary before individual risk can be assessed.

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