commentary

# HDL-C, ABCA1-mediated cholesterol efflux, and lipoprotein(a): insights into a potential novel physiologic role of lipoprotein(a)[1]

**Calvin Yeang and Sotirios Tsimikas[2]**

Division of Cardiovascular Medicine, University of California San Diego, Sulpizio Cardiovascular Center, La Jolla, CA

Lipoprotein(a) [Lp(a)], an atherogenic lipoprotein consisting of apo(a) covalently bound to apo B-100 of LDL, is a prevalent genetic risk factor for cardiovascular disease. Several genome wide association studies have established an association between SNPs in *LPA*, the gene encoding apo(a), and coronary artery disease and myocardial infarction (MI) (1–3). Moreover, recent Mendelian randomization studies also demonstrate that *LPA* SNPs associated with elevated plasma Lp(a) levels also predict development of MI (4, 5) and aortic valve stenosis (6, 7), supporting a role for Lp(a) as a genetically determined, independent, causal risk factor for these diseases. Elevated plasma Lp(a) is common, with 20% of the population having Lp(a) > 50 mg/dl, levels consistently associated with an approximately two-fold increased risk of MI in large prospectively followed cohorts (8, 9).

There have been several proposed mechanisms for the atherogenicity of Lp(a), including upregulation of endothelial cell adhesion molecules, activation of monocyte chemoattractant protein-1 (MCP-1; 10), increasing endothelial cell permeability, cytokine release, macrophage apoptosis (11), promoting smooth muscle cell proliferation, foam cell formation, and inhibition of fibrinolysis [reviewed in (12)]. Furthermore, Lp(a) is the major lipoprotein carrier of oxidized phospholipids (OxPL) (13) and carries these highly immunogenic and pro-inflammatory lipids on its LDL moiety as well as covalently bound to apo(a) (14). Lp(a) and OxPL are found in human atheromas, but more importantly, they are enriched in more advanced plaques compared with early lesions (15). Lp(a) and OxPL are both potent stimulators of apoptosis in endoplasmic reticulum stressed macrophages in a scavenger receptor CD36 and Toll-like receptor 2 dependent pathway (11). MCP-1, an important chemokine implicated in the development of atherosclerosis, binds to oxidized LDL in an OxPL dependent manner, and is found on human Lp(a) as well (10). As a clinical correlate to these basic investigations, OxPLs measured on apo B-100 (OxPL-apoB), which primarily reflect the content of OxPLs on Lp(a), strongly predicts anatomical disease in a variety of vascular beds as well as cardiovascular events such as cardiac death, MI, stroke, and peripheral arterial disease (9, 16–19).

Although it is clear that elevated levels of Lp(a) increase the risk of cardiovascular disease, the relationship between Lp(a) and hazard ratio for incident CVD has been shown in some studies to be "J" shaped, with decreased risk at low levels of Lp(a) (18, 20) but higher risk in patients with very low or nearly absent Lp(a). For example, in the 4S trial, there was a graded increase in risk of cardiac death in the placebo group with increasing Lp(a) levels. However, in the simvastatin arm, although there was a reduction in cardiac mortality in the study as a whole, the greatest benefit was not seen in the lowest quartile but instead in the second quartile of Lp(a), with a relative 58% reduction in total mortality. Unfortunately, due to arbitrary rather than absolute units of Lp(a) measurements, it's not possible to convert these data to mg/dl or nmol/L. In the Bruneck Study, a 'J" shape in risk of CVD and major adverse cardiac events was also noted, with patients having plasma levels between 2.7 and 6.8 mg/dl having the lowest risk, and patients with levels <2.7 mg/dl having similar numbers of events as those with levels 6.8–23.9 mg/dl, and the risk at higher levels rising significantly. In several studies, including the Emerging Risk Factors Collaboration analysis, a dip below an odds ratio of 1.00 was present for nonfatal MI and coronary and noncoronary death at ~8 mg/dl (21). Finally, in studies of successful aging beyond age 83 or in centenarians, there is an over-representation of patients not in the lowest quartiles but instead in those with more modest elevations of plasma Lp(a) (22–24). These phenomena are incompletely understood, but suggest potential beneficial effects of plasma Lp(a) at levels within the second quartile of Lp(a) among general populations, which may range from ~7.5 to 30 mg/dl (5, 18).

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[2]To whom correspondence should be addressed.
e-mail: stsimikas@ucsd.edu.

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The article published by Sharma et al. (25) in this issue of the *Journal of Lipid Research* suggests a potential mechanism for a protective feature of Lp(a). The authors propose that the OxPLs present on Lp(a) promote cholesterol efflux to apoA1 through upregulation of ABCA1. HepG2 cells exposed to Lp(a) isolated from human plasma increased expression of ABCA1 at both the transcriptional and protein levels. Furthermore, the authors demonstrate that Lp(a) enhances cholesterol efflux from HepG2 cells to ApoA1, the preferred cholesterol acceptor for ABCA1 and the principle apolipoprotein component of HDL. The authors documented that Lp(a) could be internalized by HepG2 cells, but that the cholesterol efflux effect was mediated by scavenger receptor B-1 (SR-B1), as documented by complete block of the effect by an anti-SR-B1 antibody. Preincubation of Lp(a) with an anti-apo(a) antibody to block Lp(a) holoparticle uptake did not affect ABCA1 transcript levels. In contrast, it was suggested that the effect appeared to be due to SR-B1-mediated internalization of the lipid content of Lp(a), and specifically OxPL within the lipid phase, as the addition of the monoclonal antibody E06, which specifically binds to the phosphocholine (PC) head group of oxidized but not native PC containing phospholipids (26–28), abolished the upregulation of ABCA1 by Lp(a). However, experiments incubating Lp(a) with E06 alone to assess the effect on ABCA1 or on efflux capacity were not reported.

The novel findings by Sharma et al. suggest a physiologic role for Lp(a) as a positive regulator of HDL metabolism, and further suggest that this role is dependent on its OxPL content and mediated via the SR-B1 receptor, which was previously shown to bind OxPL with high affinity (29). However, the association between HDL-cholesterol (HDL-C) and Lp(a) appears quite modest at the clinical level and it's not clear if this has physiologic consequences. For example, in a study involving 3,481 patients from the multi-ethnic Dallas Heart Study, baseline levels of Lp(a) ($r = 0.15$, $P < 0.001$) and OxPL-apoB ($r = 0.15$, $P < 0.001$) correlated weakly but in a highly significant manner with HDL-C (30). Furthermore, in the Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering trial of 2,342 patients with acute coronary syndromes, baseline levels of Lp(a) ($r = 0.10$, $P < 0.001$) and OxPL-apoB ($r = 0.06$, $P = 0.006$) correlated weakly but in a highly significant manner with HDL-C (31). The authors of the current study also note that Lp(a)-cholesterol [Lp(a)-C] levels correlated with HDL-C with an R-value of 0.46 in a cross-sectional study of 121 obese African American children (32). However, in that study, Lp(a)-C was assayed by Vertical Auto Profile (VAP), a technology that may not accurately reflect Lp(a) mass levels assayed by traditional immunoassays or accurate predictive value of cardiovascular risk (33). For example, Lp(a)-C measured by VAP, unlike Lp(a) mass, was not significantly associated with cardiovascular risk after multivariate analysis in the Framingham Offspring Study (34). VAP resolves plasma lipoprotein species utilizing density gradient ultracentrifugation in a single tube spin, and given the significant overlap between the densities of Lp(a) and HDL, the resolution of these two lipoproteins for downstream cholesterol measurement may be suboptimal.

Another important finding in the current study by Sharma et al. is that the uptake of both the lipid and protein components of Lp(a) by HepG2 cells are blocked by an anti-apo(a) antibody. This is consistent with in vivo data demonstrating that apo(a) competitively inhibits the plasma clearance of Lp(a) in mice (35). Although it has been more than 50 years since the discovery of Lp(a) (36), the receptor(s) involved in Lp(a) uptake are still not well defined. Using [$^{131}$I]tyramine cellobiose labeled Lp(a), which tracks the clearance of the protein of Lp(a), Cain et al. (35) showed that this lipoprotein is predominately cleared by the liver in vivo. Given that LDL is an essential component of Lp(a), the LDL receptor (LDL-R) has been an attractive candidate for the Lp(a) receptor. The LDL-R has been implicated in Lp(a) clearance in HepG2 cells (37) and LDL-R overexpressing mice (38), possibly through a bystander effect where apoB-100 of Lp(a) is recognized by LDL-R leading to internalization of Lp(a). However, Lp(a) clearance is unaffected by LDL-R deficiency in humans (39) or mice (35), suggesting that the overall magnitude of this pathway appears to be modest in vivo, and it is likely that the apo(a) moiety is mostly responsible for receptor-mediated catabolism of Lp(a), as suggested by this study.

Apo(a) is a highly glycosylated protein, with up to 30% of its mass composed of carbohydrates that are rich in sialic acid (40). Apo(a) has potential to be a ligand for the asialoglycoprotein receptor (ASGPR), but its role appears minor. The ASGPR is expressed in the liver and removes galactose-terminated asialoglycoproteins from circulation. Lp(a) catabolism was delayed in ASGPR-deficient mice, and moreover, accumulation of [$^{131}$I]tyramine cellobiose labeled Lp(a) in ASGPR-deficient livers was significantly lower compared with livers from wild-type mice (41). However, the rate of catabolism of Lp(a) in wild-type mice was very similar to that of ASGPR-deficient mice, with greater than 90% of Lp(a) cleared from the plasma at 22 h postinjection (41), suggesting that there are other receptors involved in this process.

Also not fully understood is whether Lp(a) is catabolized as a particle or, if instead, there are separate kinetics for the clearance of its two major protein moieties, apoB-100 and apo(a), as well as its lipid moieties. In their study, Sharma et al. (25) propose that SR-B1 mediates selective uptake of OxPL in lipid phase from Lp(a). Prior reports have demonstrated that SR-B1 binds to and internalizes the lipid and protein components of Lp(a) (42). However, when Lp(a) was dual-labeled with [$^{3}$H]cholesterol-ether and iodine-labeled protein was added to cells overexpressing SR-B1, there was greater uptake of lipid compared with protein, supporting selective uptake of lipid from Lp(a) and suggesting separate mechanisms for Lp(a) lipid and holoparticle internalization. The OxPLs on Lp(a) are present in two compartments: the lipid phase, where they could be readily mobilized both to and off the Lp(a) particle (e.g., into cells), and a second compartment that is covalently bound to apo(a), where their movement would likely be more restricted and tied to apo(a) movement

(13, 14). Both pools of negatively charged OxPL can potentially bind to SR-B1 with high affinity (29) and thus mediate uptake and/or cholesterol efflux. Repeating these experiments with mutant apo(a) constructs that either contain or lack OxPL (14) would be useful to further tease out the role of OxPL on Lp(a) in SR-B1. Finally, injection of [$^3$H]cholesterol-ether labeled Lp(a) into control and transgenic SR-B1 mice demonstrated greater hepatic uptake of label in transgenic mice, and in comparable experiments, decreased hepatic uptake in SR-B1 knockout mice. In that study, nonSR-B1 receptor pathways accounted for 65% of Lp(a) lipid uptake, again suggesting multiple pathways of Lp(a) catabolism. Future studies should carefully delineate how the other potential receptors described above, as well as other receptors implicated in Lp(a) catabolism are involved in the uptake of the cholesterol ester, OxPL, apo(a), and LDL components of Lp(a). These include plasminogen receptors, containing C-terminal lysine residues (43) that may bind apo(a) through its lysine binding sites (37), LRP1 (44), megalin/gp330 (45), the VLDL receptor (46), and CD36. The overall relative contribution of each of these receptors in normal metabolism, including sites other than the liver as well as in disease states such as renal failure, also needs to be determined.

The authors of this well-done study have provided insights into a potential novel role for Lp(a) as a mediator of cholesterol efflux, and additionally, raised important questions regarding how Lp(a) is catabolized. Although the data presented here in a cell culture model is convincing, the role of Lp(a) and its associated OxPL in cholesterol efflux in humans will need to be evaluated. One way this can be done is to examine large databases where plasma levels of Lp(a) and OxPL-apoB can be correlated with reported cholesterol efflux assays and also linked to outcomes. Convincing data would be that Lp(a) positively correlated with cholesterol efflux and this in turn modified the risk of CVD mediated by Lp(a). However, because these assays deplete apoB prior to measurement of efflux (49), and along with it Lp(a), they would not be informative as to a possible role of Lp(a) in modulating efflux. An alternative way to further study this would be to modify the current methodology by manipulating human plasma samples as agents for efflux from labeled cholesterol-loaded macrophages (47). For example, one could study efflux before and after selectively precipitating Lp(a) to determine its role, if any, in such efflux assays, and by omitting chemical upregulation of ABCA1, which is required for the Lp(a) mediated efflux described in this report. This will provide further understanding of the contribution of varying levels of plasma Lp(a) on cholesterol efflux in humans.

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