Brief Review

Lipoprotein(a)
An Elusive Cardiovascular Risk Factor

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Abstract—Lipoprotein (a) [Lp(a)], is present only in humans, Old World nonhuman primates, and the European hedgehog. Lp(a) has many properties in common with low-density lipoprotein (LDL) but contains a unique protein, apo(a), which is structurally different from other apolipoproteins. The size of the apo(a) gene is highly variable, resulting in the protein molecular weight ranging from 300 to 800 kDa; this large variation may be caused by neutral evolution in the absence of any selection advantage. Apo(a) influences to a major extent metabolic and physicochemical properties of Lp(a), and the size polymorphism of the apo(a) gene contributes to the pronounced heterogeneity of Lp(a). There is an inverse relationship between apo(a) size and Lp(a) levels; however, this pattern is complex. For a given apo(a) size, there is a considerable variation in Lp(a) levels across individuals, underscoring the importance to assess allele-specific Lp(a) levels. Further, Lp(a) levels differ between populations, and blacks have generally higher levels than Asians and whites, adjusting for apo(a) sizes. In addition to the apo(a) size polymorphism, an upstream pentanucleotide repeat ($TTTTA_n$) affects Lp(a) levels. Several meta-analyses have provided support for an association between Lp(a) and coronary artery disease, and the levels of Lp(a) carried in particles with smaller size apo(a) isoforms are associated with cardiovascular disease or with preclinical vascular changes. Further, there is an interaction between Lp(a) and other risk factors for cardiovascular disease. The physiological role of Lp(a) is unknown, although a majority of studies implicate Lp(a) as a risk factor. **(*Arterioscler Thromb Vasc Biol*. 2004;24:2219-2226.)**

Key Words: atherosclerosis ■ genetics ■ blacks ■ lipids

Lipoprotein(a) [Lp(a)] was first described ≈40 years ago, and interest in this entity is largely derived from its putative role as a cardiovascular risk factor.[1–3] Underlying this concept is the realization that Lp(a) has many properties in common with low-density lipoprotein (LDL), a well-established atherogenic factor for coronary artery disease.[2–5] Thus, the composition of the lipid moiety of Lp(a), including its cholesteryl ester-rich core, is similar to that of LDL, and the density distribution of the lipid moiety of Lp(a) in a given subject closely mirrors that of LDL.[6] Furthermore, like LDL, each particle of Lp(a) has 1 molecule of apolipoprotein B-100 (apo B-100); both apolipoprotein B (apoB) and the lipid core are pro-atherogenic.[7] Also, Lp(a) clearance rates are similar to those for LDL.[8,9] However, Lp(a) contains a unique protein, apolipoprotein(a) [apo(a)], which is structurally different from other apolipoproteins, having a hydrophilic, carbohydrate-rich structure with no amphipathic helices.[5,10,11] Apo(a) is linked to apoB through a single disulfide bond connecting their C-terminal regions[12–15] (Figure 1).

The presence of apo(a) influences to a major extent metabolic and physicochemical properties of Lp(a).[16–18] Notably, the cysteine residue in apoB involved in the covalent bond between apoB and apo(a) is close to the postulated LDL receptor-binding region of apoB.[19,20] It appears from many clinical studies that Lp(a) levels are not affected by LDL receptor activity,[16,21,22] suggesting that the large, carbohydrate-rich apo(a) protein introduces a charge and/or steric interaction affecting the binding potential of apoB in Lp(a) for the LDL receptor. This could at least partly explain why Lp(a) plasma levels are mainly determined by the synthetic rate in contrast to LDL in which catabolism through the LDL receptor is an important regulator of plasma levels, although overall clearance rates are similar for the 2 lipoprotein fractions.[3,8,9] Lp(a) levels are particularly affected by apo(a) synthetic rate, which is subject to strong genetic regulation. Because of this strong genetic impact, Lp(a) plasma levels are affected only to a minor extent by age, sex, and environmental factors.[3]

Lp(a): Molecular Properties

Lp(a) is very heterogeneous and the underlying reasons for this heterogeneity were uncovered by the elegant work on the gene structure of apo(a) by Lawn, Scanu, and their collaborators.[23] They reported an analogy between the apo(a) and plasminogen genes; both genes have coding sequences for loop structures stabilized by intrachain disulfide bonds, so-

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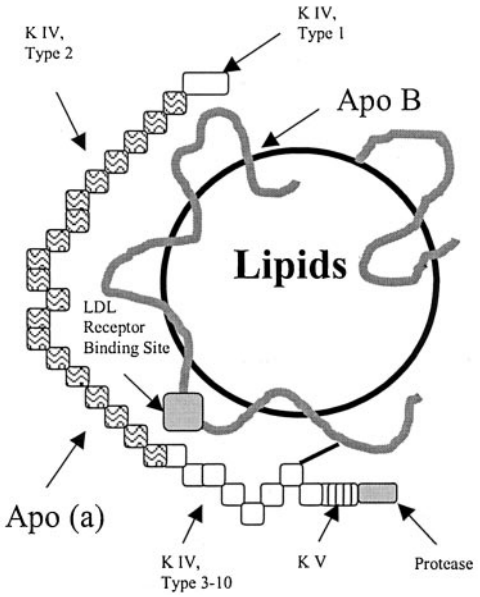

Figure 1. Model of Lp(a). The LDL-like moiety consists of a lipid core of cholesteryl esters and triglycerides surrounded by a surface layer of phospholipid and free cholesterol. In addition to lipids, it also contains one molecule of apolipoprotein B, which is linked to apolipoprotein(a) through a single disulfide bond. The putative LDL receptor binding domain of apoB is shown. The apo(a) moiety consists of a single copy of kringles KIV, types 1 and 3 to 10, kringle V, and a protease domain analogous to plasminogen. In addition, it contains multiple copies of kringle IV, type 2.

called kringle (K) domains. The plasminogen gene contains coding sequences for 5 different K domains (K1 to K5), and 2 of these are present in the apo(a) gene, K4 and K5. Interestingly, the sequence coding for one of these K domains, K4, is repeated many-fold in the apo(a) gene.[3,23–26] Altogether, the apo(a) gene has 10 different types of plasminogen-like K4 domains, referred to as K4 type 1 through 10. K4 types 1 and 3 to 10 are present as single copies, whereas K4 type 2 is present as multiple copies, varying in number from 3 to >40 copies.[16,23–26] Each kringle contains ≈80 to 85 amino acids and has a molecular weight of ≈10 kDa, and the K4 repeat unit is thus unusually large. This heterogeneity in apo(a) gene size corresponds to a size variation in the apo(a) protein and apo(a) size isoforms containing from 12 to ≈50 K4 motifs have been reported, corresponding to a protein molecular weight ranging from 300 to 800 kDa.[16,27] The size variability of apo(a) impacts on Lp(a) levels; there is a general inverse relation between apo(a) size and Lp(a) levels.[13,27,28] Thus, smaller apo(a) sizes tend to correspond to higher plasma Lp(a) levels; however, this pattern is complex. For a given apo(a) size, there is a considerable variation in Lp(a) levels across individuals.

Lp(a) is found only in humans, in Old World nonhuman primates, and in the European hedgehog.[3,29,30] The hedgehog version of apo(a) appears to have evolved separately from the primate and human apo(a) versions, because it contains the plasminogen K3 domain instead of the K4 domain and is not subject to size heterogeneity.[29] Thus, although apo(a) is novel from an evolutionary standpoint, it appears nevertheless to have emerged twice.[30] Despite this, there is currently a profound lack of understanding of any physiological function for Lp(a).

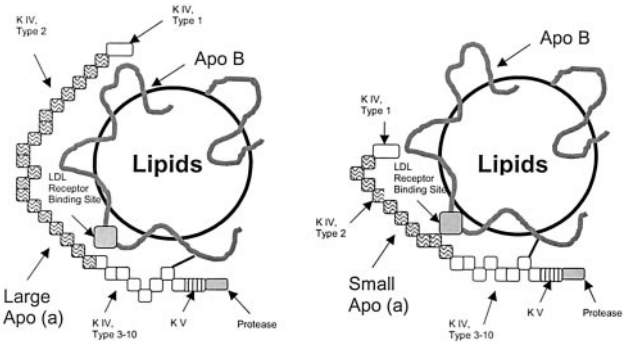

Figure 2. Two Lp(a) particles with different apo(a) sizes. Symbols as in Figure 1.

Population Studies: Apo(a) Genetics and Predictors of Lp(a) Levels

Considerable efforts have been devoted to characterizing Lp(a) levels and the frequency distribution of apo(a) sizes for different populations.[31–37] Along with the aforementioned general inverse relationship between apo(a) size and Lp(a) plasma levels, differences between populations have been noted. The most profound differences have been noted between blacks and other populations, including Asians and whites.[31–37] Notably, as a group, blacks have substantially higher Lp(a) levels than do whites or Asians, and this difference is not explained by differences in apo(a) size distribution or, so far, by other genetic factors.[38–40] This apparent paradox was addressed by Marcovina et al, who demonstrated that blacks had higher mean Lp(a) levels than whites adjusting for apo(a) sizes.[41] In particular, the interethnic difference was considerable over mid-size apo(a) ranges. This finding has been confirmed in other studies, although the reasons for this difference remain unknown.[39,40] Apart from clarifying the role of apo(a) size variation across populations, these results demonstrate the importance of assessing apo(a) allele-specific Lp(a) levels. Because homozygosity for apo(a) size is rare, most subjects have Lp(a) particles with 2 different size apo(a), and the plasma Lp(a) level is the sum of Lp(a) carried in the 2 Lp(a) populations (Figure 2). Although smaller size apo(a) frequently is associated with higher Lp(a) levels, this relation is far from absolute, and for a given subject, the relative contribution of each apo(a) size isoform to the overall plasma Lp(a) level can vary substantially.[37] Therefore, assessment of apo(a) size isoform-specific Lp(a) levels provides additional information beyond plasma Lp(a) levels.

In most previous studies, Lp(a) levels have been expressed in mass units, usually in mg/dL. When comparing Lp(a) and LDL cholesterol in assessing cardiovascular risk, it should be noted that although LDL is expressed as cholesterol levels, Lp(a) level measurements reflect particle concentrations, including both lipid and protein components. The use of mass units for Lp(a) has also required an assumption of a particular apo(a) mass, ie, ignoring apo(a) size variation. The use of molar units (eg, nmol/L) is therefore preferable and this is

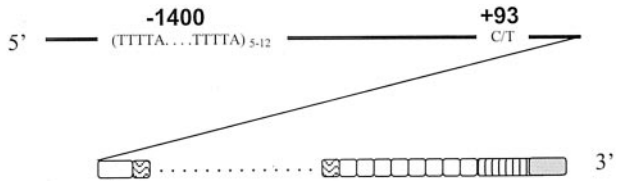

Figure 3. Upstream polymorphisms of the apo(a) gene. The PNR polymorphism is indicated by the variable presence (n=5 to 12) of TTTTA repeats at position −1400, and the C/T polymorphism represent a single nucleotide polymorphism in the promoter region of the apo(a) gene. The variability of KIV type 2 repeats of the apo(a) gene is indicated by the dotted line. Symbols for kringle repeats as in Figure 1.

facilitated by recent progress in the standardization of Lp(a) measurements.[42]

Because there is profound interindividual variation in Lp(a) levels for a given apo(a) size, suggesting that factors beyond gene size predict plasma levels, interest has focused on other apo(a) gene variations. Several polymorphisms in the apo(a) gene have been reported. Of these, a C/T variation in the promoter region of the apo(a) gene and a pentanucleotide repeat ($TTTTA_n$) ≈1 kb upstream of the apo(a) gene have been studied in this regard[43–49] (Figure 3). Of note, very few blacks carry the T allele, suggesting that the presence of this allele in the black population reflects white ancestry. Whereas experimental data linked these variations to Lp(a) levels,[43,46] findings limited to a single locus need to be interpreted with caution in the presence of linkage disequilibrium. We and others have found evidence of linkage disequilibrium for both blacks and whites between the C/T, $TTTTA_n$ polymorphism, and apo(a) size, albeit to a different degree in the 2 ethnic groups.[47–51] When taking the apo(a) size polymorphism into account, the $TTTTA_n$ polymorphism, but not the C/T polymorphism, was found to affect Lp(a) levels.[47,50,51]

Of note, although many studies have addressed differences between blacks and whites, population differences with regard to Lp(a) and apo(a) size are not limited to these groups. Differences in both Lp(a) levels and apo(a) size distribution have been noted among Asian populations.[52–56] Thus, whereas East Asians have been reported to have a relatively narrow apo(a) size distribution and low Lp(a) levels, South Asians have higher mean Lp(a) levels.[52–56] Further studies of the genetic variability of apo(a) size and Lp(a) levels across different populations are clearly warranted and may help us understand both the evolutionary pattern and regulation of this intriguing molecule, as well as shed light on the contribution of Lp(a) to the risk for cardiovascular disease.

Cardiovascular Risk Properties: Clinical Studies

Many clinical studies of coronary artery disease, cerebrovascular disease, and peripheral artery disease have been undertaken to assess the association of Lp(a) with disease. In numerous but not in all studies, mainly in white populations, elevations of plasma Lp(a) levels have been significantly correlated with coronary artery disease.[57–70] It has proven more difficult to detect an association between Lp(a) and cardiovascular disease among blacks;[71,72] however, using assessment of apo(a) size allele-specific Lp(a) levels as discussed, we found an association between cardiovascular disease and Lp(a) among black and white men with small apo(a) sizes.[38] Further, the possibility that Lp(a) levels could be increased secondary to cardiovascular disease has been raised, implying that an increased Lp(a) level could be a result of disease rather than a part of the causal pathway. Studies in model systems demonstrating a stimulation of apo(a) secretion from monkey hepatocytes by interleukin (IL)-6 have provided some support for this concept.[73] However, the role of Lp(a) as an acute phase reactant has not been universally confirmed, and reductions in Lp(a) after estrogen treatment did not correlate with changes in acute phase proteins.[74–76] Recently, data supporting the possibility that Lp(a) might induce IL-6 formation in monocytes were published, suggesting other possible links between Lp(a) and an inflammatory response.[77] Prospective studies offer possibilities to assess more direct evidence for Lp(a) as a risk factor, and recently, 2 meta analyses have demonstrated an association of Lp(a) levels with cardiovascular disease in both retrospective and prospective studies.[78,79] However, because the majority of studies on Lp(a) have been performed in white populations, prospective studies in other populations are needed. Evidence for an interaction between Lp(a) and other established or emerging risk factors for cardiovascular disease, such as LDL cholesterol, high-density lipoprotein cholesterol, and homocysteine, have also been found.[80–83] In support of a pro-atherogenic role, Lp(a) has been detected in the vessel wall, where it appears to be retained more avidly than LDL.[84–86] Further studies are warranted in clarifying the interaction of Lp(a) with elements of the vascular wall. Furthermore, based on the similarity between apo(a) and plasminogen, it has been suggested that Lp(a) may be an interloper in the fibrinolytic system.[87] Recent clinical studies have provided support for this hypothesis because Lp(a) was reported to attenuate fibrinolysis and promote coagulation.[88–90] Collectively, these results support a pro-atherogenic/thrombotic role for Lp(a).

Cardiovascular Risk Properties: Animal Models and In Vitro Studies

The presence of apo(a) only in humans and Old World primates have limited the use of animal models to explore the role of Lp(a) as a risk factor. To address this void, transgenic animal models have been created using mice and rabbits.[91–96] Initial attempts to generate a transgenic model for Lp(a) relied on the formation of this particle from human apo(a) and murine apoB. Although murine apoB did not form an Lp(a) complex with human apo(a), important insights into predictors of Lp(a) formation were gained from these studies.[91] In subsequent studies, animals transgenic for human apo(a) and apoB, allowing in vivo formation of a circulating Lp(a) particle, were used.[92,93] Somewhat contradictory results have been reported from these experiments; an increase in aortic atherosclerosis was reported by Rubin et al,[93] whereas no significant increase was reported in studies by Hobbs et al.[92] A number of factors could have contributed to the discordant results, such as different feeding conditions, varying genetic strains, and the actual apo(a) construct used. In more recent

studies, presence of atherosclerosis in transgenic mice fed a normal diet has been reported.[94] Studies in rabbits transgenic for Lp(a) have also provided support for a pro-atherogenic role.[95,96] In addition, studies in transgenic mice as well as from an arterial injury model in cynomolgus monkeys have provided support for a prothrombotic and/or antifibrinolytic role of Lp(a).[83,97,98]

Apo(a) and Cardiovascular Disease: Influence of Apo(a) Size

Atherogenicity associated with Lp(a) could be caused by risk associated with the LDL moiety, with the apo(a) moiety, or from their unique combination in Lp(a). Because there is a substantial size heterogeneity of apo(a), and smaller apo(a) sizes are associated with higher plasma Lp(a) levels, the possibility that size variation of apo(a) could be associated with cardiovascular disease has been investigated in a number of studies.[99–109] This raises the question whether such an association simply would be caused by higher Lp(a) levels commonly carried by Lp(a) particles with smaller apo(a), or whether the size variation is independently important. In several of the early studies on apo(a) size and cardiovascular disease, the technique available permitted the resolution of a limited number of apo(a) size isoforms preventing comprehensive analysis of this issue.[103,109] This problem was largely resolved by the introduction of a high-resolution technique by Kamboh et al, later refined by Marcovina et al.[110,111] Using these techniques, which allow for detailed apo(a) isoform separation, small apo(a) size has been associated more consistently with cardiovascular disease in men. Studies have shown that total Lp(a) levels in individuals who carry at least 1 small isoform are associated with cardiovascular disease or with preclinical vascular changes.[99,107,112,113] These results suggest strongly that Lp(a) particles that carry small apo(a) molecules are the appropriate risk factor. We have reported that the small apo(a) molecule is not always the dominant form of Lp(a)—quite frequently, the larger apo(a) molecule is present in greater amount.[37] Using pulsed-field electrophoresis of DNA, we found in a number of individuals with a single apo(a) isoform that the smaller allele was not expressed. Thus, use of isoform-specific or allele-specific levels may be more informative in assessing Lp(a) as a risk factor.[38,112] This further implies that determination of predictors of allele-specific apo(a) levels would be of interest in relation to Lp(a) atherogenicity. Recently, we assessed the effect of apo(a) size together with 2 other genetic variants, the upstream C/T and pentanucleotide repeat polymorphisms, on allele-specific apo(a) levels in whites and blacks (Rubin et al, unpublished observations). In both populations, each allele size affected the level of that allele as well as that of the other allele, albeit to a smaller degree. Further, in whites but not in blacks, the pentanucleotide polymorphism affected levels. Overall, the results implicate an interaction between apo(a) size alleles as well as an influence by other genetic polymorphisms on allele-specific apo(a) levels. However, more studies are needed to confirm or refute these findings as well as the hypothesis that small apo(a) molecules convey cardiovascular risk.

Whereas an association with small isoform-specific Lp(a) levels and cardiovascular disease has been found in men, the results are less convincing in women.[38,65,114] Furthermore, although Lp(a) levels have been reported to be increased in women with myocardial infarction,[115] a recent prospective study on cerebrovascular disease demonstrated an association between Lp(a) and stroke in men but not in women.[116] This does not necessarily conflict with an association between plasma Lp(a) levels and cardiovascular disease among women, although it could suggest that any risk carried by specific apo(a) sizes may be subject to modulation by gender-specific factors. Further studies are needed to explore these apparent gender differences.

Oxidized Phospholipids: Relation to Lp(a)

Recently, a new possible mechanism for apo(a) atherogenicity has been suggested. In a series of studies, Witztum et al have demonstrated convincingly that a key oxidized phospholipid is preferentially associated with Lp(a).[117–119] Proinflammatory, oxidized phospholipids are covalently bound to kringle V in apo(a), a portion of apo(a) associated with macrophage IL-8 production.[117] These results suggest that Lp(a) may act as a preferential acceptor that tightly binds oxidized phospholipids transferred from tissues or from other lipoproteins.[119] This could imply that Lp(a) functions as a scavenger absorbing potentially deleterious oxidized lipids, preventing an increased uptake in the vessel wall of other lipoproteins, primarily LDL, containing this factor. However, the presence of oxidized phospholipids in Lp(a), potentially being taken up by the vessel wall, could also accelerate development of atherosclerosis. Because kringle V is present as a single copy in the apo(a) molecule, the results suggest an apo(a) size-independent potential for binding of oxidized phospholipids, although it is possible that apo(a) size can affect the binding site through conformational changes. Notably, Lp(a) levels have been found to be higher among white centenarians, raising the possibility that Lp(a) may serve as a longevity factor, although opposite results have been reported in a Japanese cohort.[120–122]

Approaches to Modulate Lp(a) Levels: Challenges and Possibilities

In assessing appropriate cardiovascular preventive measures, one needs to consider whether intervention to lower Lp(a) is clinically warranted. At present, Lp(a) is not an established cardiovascular risk factor and there are no guidelines recommending intervention.[42,123] Our current level of understanding would suggest that Lp(a) lowering might be beneficial in white men and some other subgroups of patients with high Lp(a) levels, but we still lack enough details on how to define such subgroups with regard to Lp(a) levels, apo(a) size, and presence of other risk factors. Additionally, the lack of knowledge of Lp(a) metabolism both regarding its formation and catabolism raises considerable challenges in devising strategies to lower Lp(a) levels.[16] Because apo(a) synthesis is of major importance in regulating Lp(a) levels, interference in Lp(a) particle formation may offer intervention possibilities.[15,124,125] Further, model studies in transgenic animals and cell cultures have suggested a hepatic elimination pathway.[126]

However, the current lack of a well-defined metabolic pathway for Lp(a) has prevented any progress regarding agents that might interfere with either formation or catabolism. At present, nicotinic acid is the only major hypolipidemic agent that has proven efficacy in lowering Lp(a) levels.[127]

Role of Lp(a) Beyond Risk: Need-Driven Evolution or Development by Chance?

The limited distribution of Lp(a) to humans, Old World primates, and, as a parallel phenomenon, to the European hedgehog, has raised considerable interest and speculation regarding a possible physiological role. This has been fueled further by the pronounced genetic variability of the apo(a) gene, which represents an unusual example of a large nucleotide repeat in a coding region. It is well-known that short nucleotide repeats in coding regions can affect mRNA amounts or protein function and result in variable disease expression—examples of this can be seen in trinucleotide repeats for genes affecting Huntington chorea and fragile X.[128,129] However, there is no evidence of evolutionary pressure to favor development of Lp(a); the existence of apo(a) does not necessarily imply a useful function. After all, a considerable number of individuals have undetectable or very low Lp(a) levels without being at any apparent disadvantage. The interesting but so-far-unresolved differences between blacks and nonblacks regarding Lp(a) levels and apo(a) size allele variation might provide a possibility to assess any advantage associated with Lp(a); however, it could also be caused by the apo(a) allele distribution in the subset of the population that left Africa and subsequently gave rise to other population groups.[130] Functions suggested as possible for Lp(a) have been as an adjunct important for wound healing and/or regulation of angiogenesis.[16,55] Although a positive function may have been important during early stages of primate evolution in strengthening possibilities of survival, subsequently the importance of such a function may have decreased. A lack of selection against the gene may have resulted in retention of the apo(a) gene. In a state of neutral evolution, it would have been possible for a variety of sizes to evolve by duplication of the K4 type 2 repeat sequence, with the larger sizes and other as-yet-unidentified changes in the promoter region leading to widely varying levels of apo(a) expression with no evolutionary disadvantage.

Thus, although a majority of studies implicate Lp(a) as a risk factor, the suggestion from some studies of a beneficial effect may suggest either a dual function, perhaps depending on external circumstances, or simply a result of a neutral evolution. Although Lp(a) continues to offer surprises, further studies are needed to resolve the secrets of this mysterious phenomenon.

Acknowledgments

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