Lipoprotein(a)
A Unique Risk Factor for Atherothrombotic Disease

Joseph Loscalzo

In 1963, Kare Berg1 immunized rabbits with human low density lipoprotein (LDL) and identified a genetic variation in the anti-LDL antibody response. He attributed this genetic variation to a unique fraction of LDL that he termed lipoprotein(a) (Lp[a]), and he believed that this trait was transmitted in an autosomal dominant fashion. Over the subsequent two decades, data obtained from several groups2-5 demonstrated that elevated serum levels of Lp(a) correlate with an increased risk of atherosclerotic vascular disease. The mechanism(s) by which Lp(a) confers this increased risk has eluded identification; however, recent observations on the unique structural features of Lp(a) shed light on some possible explanations for its atherogenic potential and highlight its pathophysiologic role at the interface of atherosclerosis and thrombosis.

Lp(a) and Atherosclerotic Risk

Several laboratories6,7,8 simultaneously reported in 1972 the association between coronary artery disease and a plasma lipoprotein fraction migrating as a pre-beta, band on agarose gel or cellulose acetate electrophoresis. Shortly thereafter, this pre-beta, lipoprotein was identified as Lp(a)9 and was shown to be qualitatively associated with the manifestations of coronary artery disease.9,10 Subsequent quantitative studies have confirmed this association both retrospectively9-11 and prospectively.6 A separate prospective analysis likewise documented an association in patients with cerebrovascular disease.12

In the prospective analysis of Dahlen and colleagues,6 Lp(a) was shown to be an independent risk factor for the presence of coronary atherosclerosis, conferring a relative risk ranging from 1.6 to 3.6. An apparent threshold for coronary risk occurred at Lp(a) levels of 30 to 40 mg/dl, and such levels were observed in approximately 20% of the subjects studied. Multivariate analysis showed that the Lp(a) level as a predictor of the presence of coronary artery disease was comparable in magnitude to the well-established risk factors of total and high density lipoprotein (HDL) cholesterol. Subgroup analysis showed that Lp(a) levels were particularly powerful as predictors of the presence of angiographic coronary disease in women of all ages and in men younger than 56 years of age. Similar data were obtained in a parallel study in Hawaiian men of Japanese ancestry13 that showed the generalizability of the atherosclerotic risk imparted by elevated levels of Lp(a) to non-occidental populations.

In addition to increasing the risk of developing atherosclerosis in native vessels, elevated levels of Lp(a) also impart a risk of stenosis in vein grafts after coronary artery bypass surgery14: the mean Lp(a) level in patients with stenoses was almost double that in patients without graft stenoses (32±33 vs. 17±23 mg/dl, respectively, p=0.002). Furthermore, in a recent study with immunohistochemical analysis of vein grafts removed at reoperation, apolipoprotein (apo)(a) was found in the neointima of the graft where it colocalized with apo B.15

Early Genetic Studies of Lp(a)

The early epidemiologic studies showing the relationship between Lp(a) levels and atherosclerotic vascular disease served as the impetus for population studies aimed at characterizing the genetics of the Lp(a) trait. The earliest studies1 suggested that Lp(a) was inherited as a simple dominant Mendelian trait under the control of two alleles; however, this view lost its appeal when the population distribution of serum Lp(a) levels was found to be profoundly skewed16,17,18 in Caucasians and Orientals19 (only blacks have been found to have a normal distribution of serum levels16,17,19). Using quantitative immunochromatographic approaches, subsequent investigators suggested that Lp(a) is under polygenic control.19,21,22 A more recent series of classic family studies by Utermann and colleagues23,24,25 and Boerwinkle et al.26 revealed that Lp(a) levels are controlled by a series of autosomal alleles (Lp[a]), Lp[a]51, Lp[a]52, Lp[a]53, Lp[a]54, and Lp[a]55 at a single locus and that there is a highly significant association between specific phenotypes and plasma concentration: phenotypes S3 and S4 are associated with low plasma levels and phenotypes B, S1, and S2 are associated with high plasma levels.

This phenotypic classification of Lp(a) was based on the mobility of Lp(a) isoforms on sodium dodecyl sulfate-polyacrylamide gels. The recent abundance of informa-
tion about the structure of Lp(a) and the molecular biology of its apoprotein(s) that has been brought forth in the literature adds both significant complexity and the opportunity for clearer definition of the molecular genetics to the regulation of plasma levels of this atherogenic lipoprotein particle.

Structural Characteristics of Lp(a)

Lp(a) particles are heterogeneous in size and density and are comprised of apo B₁₀₀ linked by a single disulfide bridge to a unique apoprotein, apo(a). Apo(a) is a highly glycosylated protein (28% carbohydrate by weight) displaying size heterogeneity and molecular weights ranging from approximately 300,000 to 800,000 daltons. Heterogeneity in size is felt to be related both to polypeptide chain polymorphism and to variation in extent of glycosylation.

When exposed to a sulfhydryl reducing agent, apo(a) can be quantitatively removed from Lp(a) by ultracentrifugation. This treatment leads to the release of free apo(a) and Lp(a)-particles that float in the range of LDL. Lp(a) is somewhat larger than authentic LDL, has a surface that is completely covered by apo B₁₀₀, and contains more triglyceride than LDL. Circular dichroism studies showed that apo(a) is predominantly in the random coil configuration (71%) with 8% alpha-helix and 21% beta-sheet elements of secondary structure. Its intrinsic viscosity of 28.3 cm²/g is consistent with an extended flexible coil structure. Apo(a) is highly water soluble, and it is this property that likely accounts for the water solubility of the Lp(a) of which it is a part, despite the relative hydrophobicity of Lp(a)-. Interestingly, in a study in which a battery of monoclonal antibodies was directed against 27 different epitopes in apo B, Zawadzki and coworkers showed that the presence of apo(a) significantly altered the immunoreactivity of apo B in Lp(a) in solution compared with LDL or Lp(a)-, whereas no difference in immunoreactivity was observed when these lipoprotein particles were studied in a solid phase, plastic-bound system.

A major advance in the structural analysis of Lp(a) came about as a result of an analysis of the amino acid sequence and, subsequently, the cDNA sequence of apo(a). These data revealed that apo(a) had a striking homology to plasminogen and contained an homologous serine protease domain and multiple homologous copies of the lysine-binding "kringle" domains. Immunochemical data published 1 year later supported the antigenic similarity between apo(a) and plasminogen. In the seminal study of McLean and coworkers, a human hepatocyte library was used as a source of RNA for the isolation of cDNA clones from which the protein sequence was derived. The mRNA was found to encode a signal prepeptidtide followed by 37 tandem homologous copies (75% to 85% identity) of a sequence quite similar to the fourth kringle of plasminogen. A sequence homologous to that of the fifth plasminogen kringle (91% identity) occurs subsequently, and this is followed by an homologous serine protease domain (94% identity).

Recent Genetic Studies of Lp(a)

The apo(a) gene has been localized to the long arm of chromosome 6 (q26–27) where it is closely linked to the plasminogen gene. A recent family study showed that a restriction fragment length polymorphism of the plasminogen gene is tightly linked to the apo(a) size phenotype and to the plasma Lp(a) concentration. Taken together with the earlier data of Utermann and colleagues showing that there is an inverse relationship between apo(a) size and plasma concentration, these more recent genetic data suggest that a genetic variation in the apo(a) gene locus controls apo(a) size and Lp(a) plasma concentration. In a recent study, Gavish and coworkers have taken this analysis one step further and demonstrated that the ratio of kringle four- to kringle five-encoding domains in the apo(a) gene correlates inversely with the log of the Lp(a) plasma concentration (R² = 0.90). The mechanism by which this relationship obtains is not yet known, although these authors suggest that increased intracellular metabolism of large proteins compared with small proteins, as proposed by Goldberg and St. John, may provide one possible explanation. These interesting and unique observations notwithstanding, the fact that the correlation coefficient between the ratio of kringle four to kringle five and the plasma level of Lp(a) is not unity...
suggests that factors other than the mere number of kringle four-encoding domains may also be important in determining plasma concentrations of Lp(a).

Studies of the genetic evolution of Lp(a) are currently in their infancy. Lp(a) has been identified in nonhuman primates, in particular thales monkeys and other Old World monkeys, as well as in the insectivore, the hedgehog. It has been difficult to measure Lp(a) levels by standard immunohistochemical techniques or molecular biologic techniques in most other mammals because the highly repeated kringle four-like domains show the least sequence conservation, according to Lawn and colleagues.

Synthesis of Lp(a)

The primary site of synthesis of Lp(a) appears to be the hepatocyte, although apo(a) mRNA has also been identified in testes and brain. Synthesis of apo(a) in liver is hardly surprising given that the hepatocyte is also the primary site of the synthesis of apo B100; however, synthetic sites in brain and testes are surprising and perhaps speak to the issue of a unique function of apo(a) at these sites, particularly given their relative isolation from the systemic circulation by histologic barriers (such as the blood-brain barrier), and the absence of synthesis of apo B100 at these sites.

Once synthesized by the liver, the fate of apo(a) is determined both by its covalent association with LDL and by its noncovalent associations between the resulting Lp(a) and other plasma lipoproteins. The initial observation by Bersot and coworkers that apo(a) can be found in the chylomicron remnant fraction in normolipidemic volunteers fed lard or lard and egg yolk diets suggested that apo(a) can be incorporated into triglyceride-rich particles. Prevailing opinion holds that even in triglyceride-rich particles, most, but not all, apo(a) is covalently linked to apo B100. Other studies suggest that the association of apo(a) with triglyceride-rich particles may also involve possible noncovalent associations between the lysine-rich domains of apo B and the kringle-like domains of apo(a).

Role of Lp(a) In Cholesterol Metabolism: One Potential Atherogenic Mechanism

Since Lp(a) contains an LDL component having an apo B100 moiety, early studies addressed the access of Lp(a) to LDL receptor pathways. Several groups have demonstrated that Lp(a) binds to the classic LDL receptor in cultured fibroblasts, although with a lower affinity than LDL itself; the estimated apparent Kd for Lp(a) is 9.5 nM compared with 7.8 nM for LDL, according to Krempler and colleagues. Once bound, Lp(a) inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, indicating that Lp(a) is taken up into cells and, upon releasing its component cholesterol, regulates de novo cholesterol synthesis by a similar mechanism as LDL. Fractional catabolic rate studies of Lp(a) in normolipidemic individuals and in patients with familial hypercholesterolemia suggest that Lp(a) is removed from plasma by similar mechanisms as LDL. Since native Lp(a) is not quite as good a ligand for the LDL receptor as LDL itself, the prevalent presumption has been that Lp(a) may be preferentially taken up by the scavenger pathway. Cell culture studies with macrophages derived from peripheral blood monocytes have failed to support this hypothesis. A recent study by Haberland and colleagues, however, showed that malondialdehyde modification of Lp(a) increases uptake and degradation 60-fold over that of native Lp(a). These observations are consistent with the view that modified LDL is atherogenic and, thereby, suggest a mechanism by which Lp(a) may contribute to atherogenic foam cell formation. The potential importance of these in vitro mechanisms of atherogenesis in vivo is indicated by the observations that Lp(a) is significantly less efficiently cleared by the liver than is LDL with estrogen-induced apo B/E receptor up-regulation and that familial hypercholesterolemia and atherogenic apo(a) phenotypes synergistically elevate plasma Lp(a) levels.

One additional possible mechanism by which Lp(a) might facilitate atherogenic processes is through receptor uptake of the particle by the endothelium. The studies by Cushing and colleagues and by Rath and coworkers support this view; in both arteries and vein grafts, respectively, Lp(a) was found predominantly extra-cellularly and appeared to be relatively undegraded. Thus, by transport into the subendothelial space, Lp(a) may interact with matrix constituents, undergo chemical modification, and thereby serve as a ligand for scavenger uptake by macrophages. Preliminary studies in our laboratory with endarterectomy specimens in fact demonstrate that a significant fraction of Lp(a) measured by immunohistochemical analysis is associated with tissue macrophages (unpublished observations).

Effect of Lp(a) on Fibrinolysis: A Second Potential Atherogenic Mechanism

Perhaps the most exciting aspect of the biology of Lp(a) is the recent observation that apo(a) is strikingly homologous to plasminogen. This structural similarity between an atherogenic lipoprotein and a proteolytic enzyme important for cleaving fibrin thrombi provides the first potential molecular evidence for a mechanistic link between atherosclerosis and thrombosis. Despite the structural homology to plasminogen and the preservation of the catalytic triad at the protease-equivalent domain, apo(a) does not generate plasmin-like activity when exposed to plasminogen activators because of a key substitution of serine for arginine at the equivalent activation site. Lp(a) has been shown to manifest some proteolytic activity against artificial substrates that are not susceptible to plasmin and has also very recently been shown to cleave fibrinectin, albeit very slowly.

Since Lp(a) does not appear to manifest important proteolytic activity that could influence thrombosis, alternative mechanisms by which Lp(a) might influence thrombotic events must be considered. The numerous duplicated kringle-like domains of apo(a) provide one such mechanism. Kringle, named after Danish breakfast...
rolls which they resemble, are triple-looped structures, which contain lysine-binding regions that govern their interaction with fibrin. A variety of proteins important in coagulation and fibrinolysis contain kringle domains, including prothrombin, factor XII, single-chain and high molecular weight two-chain urokinase, tissue-type plasminogen activator, and plasminogen. Of the five kringles in plasminogen, the first has the greatest affinity for fibrin, the second and third are sites of weaker affinity, and the fourth provides a site of intermediate affinity. The relative abundance of kringle four-like domains in Lp(a) suggests that one mechanism by which Lp(a) can affect thrombosis may be by binding to fibrinogen and thereby altering rates of fibrinolysis.

The amino acid sequences of the kringle four-like domains of Lp(a) are not exactly identical to that of plasminogen kringle four, and to assess the potential for fibrinogen binding, we should consider the relevant sequence similarities and differences in some detail. Molecular modeling studies in which high-resolution proton nuclear magnetic resonance techniques and energy minimization analysis is used for structural refinement suggest that the lysine (fibrin)-binding site is defined by a dipolar surface, the polar portions of which are separated by a highly conserved hydrophobic region containing aromatic residues. As a prototype kringle binding kringle, plasminogen kringle one contains anionic asp 55 and asp 57 interacting with cationic arg 34 and arg 71. Plasminogen kringle four does not contain arg 34, but the other three charged side chains are conserved. This difference between dipolar sites in kringles one and four is felt to account for their different fibrin-binding affinities. The hydrophobic aromatic residues that are believed to play an important role in fibrin binding for kringle four are trp 62, phe 64, and, especially, trp 72.

Only one of the kringles of apo(a) (kringle 37) contains the important pair of asp residues at positions 55 and 57. However, the other three kringle four-like domains of apo(a) have substitutions at position 57; however, all of the kringle four-like domains contain arg at position 31, and 31 of these contain another arg at position 71. In addition, the critical trp 72 is conserved in all of the kringle four-like domains of apo(a). Given these structural details, it would not be surprising to find that Lp(a), and apo(a) specifically, binds to fibrinogen. In fact, the Lp(a) from which the cDNA sequence was determined binds to lysine, and Lp(a) is routinely purified in particular laboratories using lysine-Sepharose affinity chromatography. Differences in affinity among the various isoforms of Lp(a) (perhaps reflecting differences in the number or sequence of kringle four-like domains), however, may account for some of the discrepancies about the interaction of Lp(a) and fibrinogen in the literature.

As implied above, we and others have been unable to identify any plasmin-like activity of Lp(a) when it is incubated with plasminogen activators. Karadi and colleagues have, however, shown that Lp(a) attenuates significantly the activation of plasminogen by streptokinase in plasma, an observation that was later expanded by Edelberg and colleagues who demonstrated that Lp(a) does so by competing with plasminogen for streptokinase.

Streptokinase is not, however, a physiologically relevant plasminogen activator, and the importance of Lp(a)’s effect on endogenous fibrinolysis was first identified by our group using tissue-type plasminogen activator (t-PA). t-PA is relatively fibrinogen-selective in that its catalytic efficiency increases dramatically (approximately 300-fold) in the presence of fibrin compared with its absence. We hypothesized that through its multiple kringle four-like domains, Lp(a) binds to fibrinogen and thereby attenuates fibrin-mediated enhancement of t-PA activation of plasminogen. This hypothesis was borne out by experiments showing that Lp(a) attenuates fibrin-dependent enhancement of t-PA conversion of plasminogen to plasmin and does so as an uncompetitive inhibitor (K_i = 15 nM). Furthermore, we showed that Lp(a) binds to fibrin, both when immobilized on an inert surface and in solution, and competes with plasminogen and t-PA for fibrin binding. None of these effects were observed with apo(a)-free LDL in parallel experiments. Lp(a) was also shown to attenuate clot lysis in plasma, and patients with elevated levels of Lp(a) were found to manifest significantly reduced endogenous clot lysis in plasma ex vivo. These results suggested that Lp(a) could attenuate (endogenous) fibrinolysis in vivo and were confirmed by Brandstrom and colleagues and lent additional support by Harpel and coworkers who showed that plasmin treatment of immobilized fibrinogen enhanced the binding of Lp(a) to that ligand. In addition to these supportive data, Wolf and coworkers recently showed that apo(a) colocalized with fibrinogen in human coronary atheromata, an ex vivo observation that points to the pathophysiologic relevance of the interaction between the atherogenic Lp(a) particle and atheroma-associated fibrinogen.

Fibrinogen is not the only site at which plasminogen activation by t-PA is enhanced; the surface of cells rich in plasminogen receptors, such as endothelial cells and mononuclear cells, provide additional vascular sites at which the catalytic efficiency of t-PA activity is stimulated. These receptors are believed to facilitate plasminogen activation, protect plasmin from inactivation in the microvascular milieu, and thereby maintain blood fluidity. Two recent reports present evidence that Lp(a) attenuates cell surface-mediated enhancement of plasminogen activation by t-PA and does so by competing with plasminogen for cell-surface binding sites. These data support the view that Lp(a) does, indeed, interfere with the normal mechanisms of fibrinolysis and, as such, may promote a prothrombotic diathesis that contributes to the evolution and clinical expression of atherosclerotic disease independent of its effects on cholesterol metabolism. The relationships among these different mechanisms of atherothrombogenesis by Lp(a) are depicted in Figure 2.

**Treatment of Elevated Lp(a) Levels**

Given the epidemiologic relationship between Lp(a) and atherosclerotic vascular disease, the patho-
There have as yet been no studies that demonstrate that lowering elevated Lp(a) levels can reduce risk, however, by analogy with other risk reduction studies, it is reasonable to conclude that a similar beneficial effect may be realized with reduction of Lp(a) levels. Two problems hinder the achievement of this goal: until recently, measurement of Lp(a) levels has been confounded by antibody cross-reactivity with plasminogen, and there has not been any simple means to effect significant lowering of elevated Lp(a) levels with standard hypolipidemic agents. The first problem has been best addressed and surmounted by the development of a very specific enzyme-linked immunosorbent assay by Fless and colleagues. These investigators confirmed the skewed distribution of Lp(a) levels in their study population of 84 patients, and found that one-third of the patients had less than 1 mg/dl of Lp(a) protein. The mean level was 3.2 mg/dl of Lp(a) protein with a range of 0.045 to 13.3 mg/dl. The lower limit of detection in this assay was 0.03 mg/dl, and the conversion factor for calculating the concentration of Lp(a) lipoprotein from these direct protein measurements was 4.2.

As to treatment, HMG CoA reductase inhibitors and bile acid sequestrants have no effect. Niacin and niacin, however, have shown some effect when used separately or in combination. The potential benefits of lowering Lp(a) levels for the progression of atherothrombotic disease have, as yet, not be addressed.

**Remaining Questions**

Despite the significant body of investigative effort directed toward understanding this unique lipoprotein, many questions remain unanswered at the current time. Chief among these is simply: What is the physiologic function of Lp(a)? Brown and Goldstein have speculated that Lp(a) provides a carrier system for LDL to sites of tissue injury by binding to fibrin and liberating LDL to proliferating fibroblasts. The logic of this reparative function notwithstanding, the abundance of apo(a) mRNA in tests and brain suggests that alternative functions must also be entertained. In addition to the general question of physiologic function, questions about the role of Lp(a) in atherogenesis also remain. What function of Lp(a)—delivering cholesterol (perhaps through the scavenger pathway to cells in the vessel wall) or promoting thrombosis by limiting fibrinolysis—is most important? Does Lp(a) have more of a role in the chronic evolution of atherothrombotic disease, or is its thromboregulatory role more important in preventing rapid lysis of thrombus at sites of acute plaque activation and rupture? Perhaps the elevated levels of plasminogen activator inhibitor activity measured by Hamsten and colleagues in young survivors of myocardial infarction may represent elevated levels of antifibrinolytic Lp(a). Clearly, much additional investigative effort will need to be applied to delineate the answers to these important questions.

**Conclusions: Interaction of Atherosclerosis and Thrombosis**

Over 20 years ago, Haust and colleagues showed that human fatty streaks removed at autopsy contained large amounts of fibrin. Since that time, several determinants of thrombosis have been implicated in atherogenesis, including platelets, von Willebrand factor, and dysfunctional endothelial cells. These prothrombotic tendencies are believed to contribute to the chronic evolution of atheromata during its clinically quiescent phase. The ultimate clinical expression of atherosclerotic disease represents a separate, acute event during which...
the atheroma becomes "active." With activation, the plaque ruptures, exposing its potently prothrombotic subendothelial matrix, an event that leads to the exuberant production of (sub)occlusive thrombus. It therefore should come as no surprise that prothrombotic risks of (clinically apparent) atherothrombotic disease may be important both during the clinically quiescent, prolonged evolutionary phase and during the acute, clinically active phase. Lp(a) may be one element conferring prothrombotic risk that contributes both to chronic and acute atherothrombogenesis. Future studies should clarify these issues of a historically important, but only recently emphasized, association of two critical pathogenic processes in vascular disease.

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J Loscalzo

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