THE ROLE OF LIPOPROTEIN(a) IN
ATHEROGENESIS AND
THROMBOSIS

Katherine A. Hajjar, M.D., and Ralph L. Nachman, M.D.

Departments of Pediatrics and Medicine, Cornell University Medical College, 1300 York Avenue, New York, New York 10021

KEY WORDS: fibrinolysis, growth factors, lipid metabolism, polymorphism, vascular biology

ABSTRACT

Lipoprotein(a) [Lp(a)] represents an important independent risk factor for atherosclerotic cardiovascular disease. Lp(a) constitutes a class of low-density lipoprotein-like particles that are structurally heterogeneous due to variability within the distinguishing apoprotein, apolipoprotein(a) [Apo(a)]. Apo(a) bears a high degree of homology to the fibrinolytic zymogen, plasminogen, the parent molecule of the serine protease plasmin. Apo(a) contains a variable number of tandemly repeated triple-loop units called kringles, which appear to mediate Lp(a)’s interactions with fibrin and cell surface receptors. Although the mechanism of its atherogenicity is unknown, Lp(a) has been implicated in the delivery of cholesterol to the injured blood vessel, in blockade of plasmin generation on fibrin and cell surfaces, and as a stimulus for smooth muscle cell proliferation. In addition, new members of the plasminogen/Apo(a) gene family have been defined, creating a potential link between Lp(a) and the control of angiogenesis in both health and disease. Pharmacologic therapy of elevated Lp(a) levels has been only modestly successful; apheresis remains the most effective therapeutic modality.

INTRODUCTION

In 1963, lipoprotein(a) [Lp(a)] was identified by Kare Berg as an antigenic determinant defined by heterologous rabbit antisera raised against human low density lipoprotein (LDL) fractions (1). Over the next two decades, Lp(a) came to be associated with atherosclerotic vascular disease (2–4) and in the
past ten years has assumed the status of an independent risk factor for atherosclerotic myocardial and cerebral infarction (5–9). Since the elucidation of the basic structure of Lp(a), considerable progress has been made toward understanding the mechanism of its atherogenicity.

HETEROGENEITY OF Lp(a)

Lp(a) represents a class of structurally and functionally diverse lipoprotein particles closely related to the major cholesterol transporters, LDL, in plasma (10). Ranging in density from 1.05–1.1 gm/ml, Lp(a), like LDL (density 1.03–1.06 gm/ml), possesses a cholesterol-phospholipid core and a closely associated protein called Apo B100. Lp(a) differs from LDL, however, in that each lipoprotein particle contains one copy of an additional protein of the apoprotein(a) [Apo(a)] family bound to Apo B100 by a single disulfide link-
Apo(a) represents a heterogeneous class of glycoproteins that vary in molecular mass from ∼280 to ∼700 kDa (12–14). Structural variability in Apo(a) is mainly due to polymorphisms in the number of repeat sequences and corresponding polypeptide chain length (15), with minor changes contributed by differences in glycosylation (16).

In 1987, isolation and sequencing of the complementary (c) DNA for Apo(a) revealed striking sequence homology with plasminogen, the parent zymogen for the serine protease, plasmin (17, 18). The plasminogen cDNA contains a signal sequence, a tail region, five triple disulfide-loop structures called kringles, and a serine protease domain. Although it lacked kringles 1 through 3, the first Apo(a) cDNA to be isolated contained a signal sequence, 37 tandemly repeated copies of a kringle 4-like structure, a single kringle 5, and an inactive protease domain, all of which were 75–100% homologous to plasminogen sequences at the DNA level. The Apo(a) and plasminogen genes were subsequently found to be linked on chromosome 6 (19, 20), which contains at least two other plasminogen-related genes or pseudogenes (21). There are now at least six distinct members of this gene family (22, 23).

The presence of multiple kringle 4–like structures in Apo(a) is of special interest because this structure on plasminogen possesses a lysine binding site of moderate affinity, which allows plasminogen to interact with other proteins (24–27). Studies on rhesus monkey Lp(a) have provided further insight. They revealed that rhesus Lp(a) binds less efficiently than human Lp(a) to lysine sepharose and to cultured U937 cells (28). This is due to the presence of arginine rather than tryptophan at position 72 in the 37th copy of kringle 4 (K4 37), which plays a dominant role in the lysine binding function of Apo(a) (28).

Similarly, individual samples of human Lp(a) appear to vary in their ability to bind to lysine sepharose, suggesting polymorphisms that involve this kringle within the human population as well (29). Recent studies suggest in fact that Apo(a) heterogeneity does influence its ability to interfere with fibrinolysis in vitro (30).

The molecular basis of diversity in Lp(a) plasma levels has been under scrutiny for some time. Because plasminogen and Apo(a) are genetically linked on chromosome 6, they may have arisen from unequal crossing over and duplication of a common ancestral gene (19, 20). However, although plasma levels of plasminogen are relatively constant, Lp(a) levels appear to vary in a heritable fashion (31) even though rates of Lp(a) catabolism do not vary significantly among individuals (32). Though not a quantitative relationship, lower molecular mass isoforms of Lp(a) have in general been shown to correlate with higher Lp(a) levels both in humans (33) and in cynomolgus monkeys (34). In humans, pulsed-field gel electrophoresis has revealed that the size of a given Apo(a) gene correlates directly with the size of the corre-
sponding Apo(a) protein, and inversely with the concentration of Apo(a) in plasma (35). Collectively, these studies lead to the conclusion that plasma Lp(a) levels are allele-specific at the Apo(a) locus. This concept was recently refined with the identification, among alleles of identical size, of single-strand DNA conformation polymorphisms that cosegregated with plasma Lp(a) levels (36). This suggests that small sequence variations within the coding portion of the gene help to determine plasma Lp(a) levels. Thus, although plasma levels are generally predictive of isoform size, they correlate best with individual alleles (37).

The recent isolation of the Apo(a) gene’s promoter region has further elucidated the genetic control of hyperlipoproteinemia(a) (38, 39). Specifically, a 1-kilobase (kb) fragment of upstream sequence was found to contain several potential cis-acting elements, including seven interleukin-6 responsive elements and three additional hepatocyte-specific transcription elements (HNF-1α, CEBP, and LF-A1) (39). In promoter constructs, deletion of the HNF-1α binding site located at bases −98 through +130 leads to an 88% reduction in expression of a reporter gene, suggesting that this transcription factor plays a dominant role in liver-specific expression of Apo(a) (40). The presence of multiple interleukin-6 responsive elements may explain the transient increase in Lp(a) levels observed during acute inflammatory states (41).

Additional 5′ flanking region polymorphisms have been identified for the Apo(a) gene. They include four alleles whose frequency appears to vary with the presence or absence of overt atherosclerosis among two distinct ethnic groups (42), and a pentanucleotide repeat (TTTTA)n, which accounts for 10–14% of Lp(a) concentration variability among European Caucasians but not South African Blacks (43). Another polymorphism in the 5′ flanking region appears to significantly influence translational efficiency (44). Thus, allelic variation in transcriptional control may contribute significantly to heritable differences in Lp(a) plasma levels.

**EPIDEMIOLOGY OF Lp(a)-ASSOCIATED ATHEROSCLEROSIS**

Many epidemiological studies have now demonstrated a close correlation between blood levels of Lp(a) above 30 mg/dl and coronary and cerebral vascular disease (45, 46). The incidence of coronary artery disease increases with elevated levels of Lp(a), an association that does not depend upon plasma LDL or cholesterol levels (47). Lp(a) levels are an independent risk factor for myocardial infarction in males under the age of 46 years (48). Lp(a) levels are inversely related to the rate of coronary artery recanalization after myocardial infarction (49); they also predict a higher rate of saphenous vein bypass stenosis (50). In individuals with high Lp(a) levels, Lp(a) is deposited more
readily into saphenous vein grafts, and the rate of deposition exceeds that of Apo B100 when corrected for the LDL level (51–53). In cardiac transplant recipients, elevated Lp(a) is a risk factor for accelerated coronary atherosclerosis, a major cause of transplant failure (54). In addition, Lp(a) is an independent risk factor for cerebral atherosclerosis (55) and infarction (56). Ample quantities of Lp(a) have been identified by immunohistochemical techniques within atheromatous lesions (57) and on the thickened coronary intima from a cardiac transplant recipient (Figure 2).

**POTENTIAL MECHANISMS OF AHEROGENICITY**

Despite clear epidemiologic evidence linking Lp(a) to atherosclerotic vascular disease, the precise mechanism for its atherogenicity is not yet clear (Figure 3). Three hypotheses have been advanced, based upon studies on (a) the role of Lp(a) in cholesterol delivery to the injured blood vessel, (b) interference by Lp(a) with plasmin formation and activity, and (c) stimulation of vascular cell proliferation by Lp(a). These themes have been explored in cell culture systems, in transgenic animals, and in clinical studies. In addition, Lp(a) may contribute to atherogenesis through its postulated role in the inflammatory response.

*Figure 2* Immunohistochemical identification of Lp(a) in an atherosclerotic coronary artery obtained at surgery from a cardiac transplant recipient. Sections were immunoperoxidase stained after reaction with a monoclonal antibody specific for Lp(a) by Western blot.
Cholesterol Delivery to Injured Blood Vessels

The earliest mechanistic studies on Lp(a) revealed a potential role in cholesterol metabolism and transport. A number of investigators have demonstrated that Lp(a) binds specifically, albeit with low affinity, to the classical LDL receptor on several cell types (58–60). A higher affinity interaction appears to take place in a murine macrophage cell line (61). In transgenic mice, which overexpress the human LDL receptor, catabolism of exogenously administered human Lp(a) was significantly accelerated (62). Upon oxidation or modifica-

![Diagram of Lp(a) and Atherosclerosis](image)

*Figure 3* Working model of Lp(a) and vascular pathophysiology. Lp(a) competes with plasminogen for binding to cell surface receptors and fibrin, preferred sites of plasminogen activation. Inhibition of plasmin generation by Lp(a) results in fibrin accumulation within atherosclerotic lesions and failure to activate transforming growth factor β (TGFβ), a modulator of smooth muscle cell (SMC) proliferation. In addition, Lp(a) may alter the endothelial cell (EC) phenotype by inducing synthesis of plasminogen activator inhibitor-type 1 (PAI-1), expression of intercellular adhesion molecule-1 (ICAM), and release of endothelium-derived relaxing factor (EDRF) (nitric oxide). [Modified with permission (122).]
tion with malonyldialdehyde, Lp(a) becomes a ligand for the scavenger receptor both in vivo and in vitro (63–65). In addition, macrophage foam cells may express a distinct Lp(a) clearance receptor that is lysine binding-site independent (66). How these various receptors are coordinated in vivo is not yet clear.

Studies in transgenic mice that overexpress Apo(a), moreover, have strengthened the hypothesis that this molecule contributes to lipid accumulation in the blood vessel wall, possibly by interacting with LDL uptake mechanisms. When transgenic mice expressing human Apo(a) were fed a lipid-rich diet, they displayed a 30-fold increase in mean lipid-staining lesion area compared with lipid-fed control litter mates (67). In addition, preincubation of cultured fibroblasts with Lp(a) enhances their uptake of LDL (68), whereas cholesterol loading of macrophages in vitro enhances internalization of Lp(a) (69). Thus, atherogenesis may be favored if Lp(a) either interferes with normal cholesterol degradation via the LDL receptor or is itself targeted to the incipient atherosclerotic plaque, possibly via the scavenger receptor on invading macrophages.

**Inhibition of Plasminogenesis on Fibrin**

The recent discovery of extensive sequence homology between Apo(a) and plasminogen (17, 18) has led to several hypotheses concerning the atherogeneity of Lp(a). These studies imply a potential link between hypofibrinolysis and atherosclerosis by suggesting that repeated subclinical thrombotic events may promote arterial injury at points of incipient plaque formation (70). Lp(a) displays no proteolytic activity except for a single, unconfirmed report that it can cleave fibronectin with low catalytic efficiency (71). However, the presence of tandemly repeated kringle 4–like domains, a lysine binding structure of intermediate affinity, led to the hypothesis that Lp(a) might mimic plasminogen in its interaction with fibrin, cell surface receptors, or other proteins. Indeed, Lp(a) has been shown to attenuate the activation of plasminogen by both streptokinase (72, 73) and tissue plasminogen activator (74). Lp(a) has been shown to compete with plasminogen for binding to fibrin (75), and to bind, like plasminogen, even more avidly to plasmin-treated fibrin (76). Deposition of Lp(a) on a fibrin surface is enhanced by the atherogenic amino acid, homocysteine, suggesting a link with hyperhomocysteinemia-associated vascular disease (77). In an animal model, furthermore, Lp(a) transgenic mice are resistant to tissue plasminogen activator (tPA)-dependent lysis of artificially induced fibrin thrombi (78). Together, these studies suggest that Lp(a) may promote atherosclerosis by impairing fibrin clearance in the injured blood vessel, or by accumulating on fibrin-containing atherosclerotic plaques (76).
Impaired Plasmin Generation on Cell Surfaces

Many cell types have recently been found to express cell surface receptors for plasminogen (79). These include gangliosides and α-enolase on monocytoid cells (80, 81), the Heymann nephritis antigen on renal epithelial cells (82), a glyceraldehyde-3-phosphate dehydrogenase-like protein on streptococci (83), glycoprotein IIb/IIIa on platelets and synovial fibroblasts (84, 85), and amphoterin on neuroblastoma cells (86). It appears that most plasminogen-binding proteins have carboxyl terminal lysine residues that interact with kringle structures of plasminogen, thereby protecting subsequently formed plasmin from neutralization by its circulating inhibitor, α₂-antiplasmin.

Among cells that assemble plasminogen and plasminogen activators, the endothelial cell has become an important paradigm because cell surface plasmin generation may contribute to key endothelial cell functions, such as non thrombogenicity and activation of growth and differentiation factors. The first endothelial cell plasminogen/tPA coreceptor was identified in the past year (Figure 4) (87). This protein, annexin II, represents the most basic (pI 8.2–8.4) member of a 12-molecule superfamily of calcium-regulated, phospholipid-binding proteins (88, 89). Several annexins are found within endothelial cells, but annexin II appears to be selectively expressed on the cell surface (87, 90, 91). Since annexin II lacks an obvious transmembrane domain (92), it seems likely that its phospholipid-binding sequences may play a central role in its stabilization at the cell surface. Annexin II possesses independent binding domains for both plasminogen and tPA, as confirmed in transfection analyses and antisense and immunoinhibition studies (93, 94). Efficient binding of plasminogen to annexin II appears to require two independent proteolytic events. The first converts amino terminal glutamic acid plasminogen to a more avid ligand, amino terminal lysine plasminogen (95, 96), and the second activates the receptor at the dibasic sequence K307–R308 (87). At another level of regulation, the thiol containing amino acid homocysteine disables the tPA binding domain of cell surface annexin II (97). Overall, annexin II accounts for at least half of the plasminogen and tPA binding sites on the surface of cultured endothelial cells.

Data from several groups have confirmed, furthermore, that the highly atherogenic LDL-like particle Lp(a) competes with plasminogen for binding to cell surfaces in general, and to annexin II in particular. In vitro, both intact Lp(a) and recombinant Apo(a) inhibited plasminogen binding to endothelial cells (57), to U937 cells (98, 99), and to platelets (100). Lp(a) also specifically inhibited tPA-dependent plasmin generation on the surface of endothelial cells (57) without blocking tPA binding to these cells (101). Additionally, Apo(a) specifically inhibits binding of plasminogen, but not tPA, to purified annexin II (Figure 5) (96). These studies provide a potential mechanistic link between
depressed plasmin formation and atherogenesis because annexin II acts as a fibrin-like cofactor, stimulating the catalytic efficiency of tPA-dependent plasminogen activation by 60-fold (102).

**Lp(a) as an Inducer of Vascular Cell Proliferation**

A third potential mechanism whereby Lp(a) may induce atherogenesis is related to its potential effect on growth factor activity and subsequent vascular cell proliferation. In vitro, Lp(a) has been shown to inhibit activation of the latent form of the differentiation/growth factor, transforming growth factor β (TGFβ), in a dose-dependent manner (103). This finding was of great interest
because previous in vitro studies had indicated that plasmin can activate latent TGFβ, an endogenous inhibitor of smooth muscle cell proliferation, by cleaving and releasing an amino terminal glycopeptide (104, 105). In further studies, Lp(a) was shown to induce proliferation of cultured human and rat smooth muscle cells, and this effect correlated with impaired activation of TGFβ (106). Analogous studies have been carried out in an animal model system whereby activation of TGFβ as well as blood vessel–associated plasmin was found to be profoundly reduced in Lp(a) transgenic mice (107).

THE PLASMINOGEN GENE FAMILY AND ANGIOGENESIS

The plasminogen gene spans 52.5 kb of DNA on chromosome 6q26–27, consists of 19 exons (108, 109), and directs expression of a 2.7-kb messenger (m)RNA (110). The Apo(a) locus, also located on chromosome 6q26–27 (19–21), lies within 50 kb of the plasminogen gene (21). The cDNA for
Apo(a) has 75–100% sequence homology to plasminogen, accounting for its ability to block plasminogen-protein interactions through molecular mimicry (17, 18). An unexpected windfall from the detailed characterization of these genes has been the discovery of several related genes or pseudogenes (Table 1). A third transcript, that of plasminogen-related gene B, encoding a putative Mr 8800 protein highly homologous to the 76 amino acid amino terminal preactivation peptide of plasminogen, was found in metastatic breast carcinoma cells (111). In the past year, moreover, four additional homologues have been identified (21). One of these, designated Apo(a)-related gene C, has a domain structure consisting of about five kringles and is transcribed in human liver (21). Three additional homologues of unknown function reside on chromosomes 2, 4, and 6 (22, 23). This clustering of genes with potentially related function is reminiscent of the developmentally regulated β-globin gene cluster on chromosome 11 (21). Needless to say, full characterization of these plasminogen/apolipoprotein-like gene products may provide new avenues for exploring the control of plasmin generation.

Two additional plasminogen/Apo(a) gene homologues, hepatocyte growth factor (HGF) and macrophage stimulating protein (MSP), have been identified on chromosomes 7 and 3, respectively (112–114). HGF stimulates epithelial cell mitosis and motility and consists of four plasminogen-like kringles plus an inactive protease-like domain. Under specific circumstances, HGF appears to be a potent inducer of endothelial cell migration, proliferation, and tubular morphogenesis (115, 116); it also induces neovascularization in rabbit cornea (117). MSP enhances the macrophage response to the chemoattractant C5a and mimics the domain structure of HGF. Whether or not HGF and MSP can modulate cell surface binding of plasminogen and Lp(a) is unknown.

Another intriguing development involving plasminogen-related molecules relates to tumor angiogenesis, and to the inhibition of metastatic tumor growth by a primary lesion (118). Serum and urine from mice bearing Lewis lung carcinomas specifically inhibited endothelial cell proliferation and angiogene-

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Kringle region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasminogen</td>
<td>6</td>
<td>1–5</td>
</tr>
<tr>
<td>Apo(a)</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>PRG-B</td>
<td>2</td>
<td>none</td>
</tr>
<tr>
<td>Apo(a)-rg-C</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Hepatocyte growth factor</td>
<td>7</td>
<td>1–4</td>
</tr>
<tr>
<td>Macrophage stimulating protein</td>
<td>3</td>
<td>1–4</td>
</tr>
</tbody>
</table>

*Plasminogen-related gene-B.

a Apo(a)-related gene-C.
sis in both in vitro and in vivo assays. The activity copurified with a Mr 38,000 protein nearly identical to an elastase-derived internal fragment of plasminogen stretching from amino acids 98 through 440. This polypeptide, dubbed angiostatin, thus consists of kringles 1–4 of plasminogen. Interestingly, its angiostatic activity was neither mimicked nor inhibited by intact plasminogen although the kringle 1–3 fragment, but not the kringle 4 fragment, inhibited endothelial cell proliferation. How angiostatin reacts with the endothelial cell to inhibit mitosis is currently unknown. This study raises the intriguing question of whether Apo(a) or other plasminogen family gene products will have related bioactivities.

The potential modulation of new blood vessel formation by members of the plasminogen/Apo(a) gene family may have profound implications in the evolution of the atherosclerotic plaque. Atherosclerotic injury to coronary arteries is associated with marked neovascularization of the artery wall by a dense plexus of microvessels derived from vasa vasorum (119). Intraplaque microvessels appear to be more prevalent within restenotic atherectomy samples than in primary lesions (120). Recent in situ hybridization studies reveal increased expression of fibrinolytic genes in association with capillary proliferation within the walls of atherosclerotic aortic aneurysm lesions. They suggest that local angiogenesis may contribute to blood vessel weakening and aneurysmal expansion (121). Thus, neovascularization of the atherosclerotic plaque may be associated with its destabilization and eventual rupture.

**Lp(a) AND INFLAMMATION**

Circumstantial evidence suggests that Lp(a) may play a role in the modulation of vascular function during inflammation. Lp(a) represents an acute phase reactant and plasma levels are transiently increased 8–11 days after acute myocardial infarction or surgery (41). Immunohistochemical techniques, furthermore, have demonstrated microvascular Lp(a) deposition in a number of inflammatory lesions, including those associated with Crohn’s ileitis, gall bladder fistulae, granulomatous lymph nodes, or pericarditis (122). It is also of interest that Lp(a) has been detected in the spiral arteries of human placenta undergoing fibrinoid degeneration in preeclamptic women (123). Lp(a) is conspicuous in the vasa vasorum of diseased coronary arteries (Figure 6), whereas it was not detectable in the microvasculature of normal tissues. Further evidence indicates that Lp(a) may activate vascular cells, inducing expression of the adhesive glycoprotein ICAM-1 (intercellular adhesion molecule-1) (124) while decreasing the endogenous vasodilator EDRF (endothelium-derived relaxing factor/nitric oxide) (125). By suppressing plasmin-mediated degradation of fibrin, Lp(a) may inhibit release of chemotactic peptides that have been postulated to stimulate cellular influx into blood vessel intima...
In addition, Lp(a) may induce endothelial cell release of the fibrinolytic inhibitor plasminogen activator-1 (127).

THERAPY OF ELEVATED Lp(a) LEVELS

With the recent identification of Lp(a) as an independent atherosclerotic risk factor, its long-standing association with atherosclerotic lesions, and recent mechanistic studies suggesting a etiologic link, it is reasonable to postulate that efforts to lower Lp(a) levels would be salutary. However, there are, as yet, no definitive studies demonstrating that reduction of elevated Lp(a) levels will reduce the risk of atherothrombotic vascular occlusion in susceptible individuals. It is clear that Lp(a) plasma concentrations vary widely among individuals. These levels are relatively resistant to environmental factors such as diet and appear to be determined almost exclusively by genetic factors.

For adequate therapy of hyperlipoproteinemia(a), two issues are pertinent. First, an accurate and efficient means of estimating plasma Lp(a) levels using...
reagents that do not cross-react with plasminogen is essential (128). It has been suggested that such an assay be applied to patients with a personal or family history of premature cardiovascular disease, established atherosclerotic cardiovascular disease and a normal lipid profile on routine analysis, a history of recurrent coronary artery stenosis, or family history of hyperliproteinemia(a) (129).

Second, more effective means of lowering Lp(a) levels are necessary. With varying degrees of success, a number of agents have been reported to lower circulating Lp(a) levels (Table 2). In a limited study, N-acetylcysteine appeared to be of some value, presumably by blocking the disulfide link between Apo B100 and Apo(a) (130). Nicotinic acid (niacin) in doses up to several grams daily may also be effective in some patients but is often poorly tolerated (131, 132). Diet, exercise, and standard pharmacologic maneuvers to lower plasma LDL may be the most efficacious approach to treating Lp(a)-initiated atherogenesis because elevated LDL levels may exacerbate the risk engendered by elevated levels of plasma Lp(a) (68). Thus, LDL reduction with hydroxymethylglutaryl-coenzyme A reductase inhibitors, fibrates, and ion exchange resins may all play a role. At present, the one—albeit costly and invasive—method of proven value is LDL apheresis, which should be reserved for individuals with extreme elevations of Lp(a) (133). A related modality, heparin-induced extracorporeal LDL precipitation, is currently under investigation (134).

UNRESOLVED ISSUES

Despite recent advances, the precise physiologic function of Lp(a) remains an enigma. There are no known clinical deficiency states relevant to Lp(a), and most animal species appear to lack Lp(a) altogether. Does Lp(a) constitute a specialized cholesterol transporter that delivers cholesterol to proliferating cells at sites of tissue injury (135)? Is it a physiologic modulator of plasmin generation? Does it control tissue remodeling or angiogenesis? Why is it synthesized in tissues like brain and testis that are sequestered behind blood-

<table>
<thead>
<tr>
<th>Table 2 Lp(a) lowering agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Estrogen</td>
</tr>
<tr>
<td>2. Tamoxifen</td>
</tr>
<tr>
<td>3. Niacin</td>
</tr>
<tr>
<td>4. Gemfibrozil</td>
</tr>
<tr>
<td>5. Omega-3 fatty acids</td>
</tr>
<tr>
<td>6. N-acetylcysteine</td>
</tr>
<tr>
<td>7. Prednisone</td>
</tr>
<tr>
<td>8. Neomycin</td>
</tr>
</tbody>
</table>
organ barriers (136)? Why is it expressed only in primates and hedgehogs (137)? Ultimately, answers to these and other questions will engender new lines of inquiry, and the undisclosed secrets of Lp(a) (45) will be revealed.

ACKNOWLEDGMENT

Work from the authors’ laboratories was supported by grants from the NIH (HL 42493, HL 46403, HL 18828).

Any Annual Review chapter, as well as any article cited in an Annual Review chapter, may be purchased from the Annual Reviews Preprints and Reprints service.

1-800-347-8007; 415-259-5017; email: arpr@class.org

Literature Cited


34. Azrolan N, Gavish D, Breslow JL. 1991. Plasma lipoprotein(a) concentration is controlled by apolipoprotein(a) (apo(a)) protein size and the abundance of hepatic apo(a) mRNA in a cynomolgus monkey model. *J. Biol. Chem.* 266:13866–72.


45. Liu AC, Lawn RM. 1994. Lipoprotein(a)


70. Fless GM, Scann AM, et al. 1991. Lipoprotein(a) fibrin binding and
plasminogen activation. *Arteriosclerosis* 10:240–45


102. Cesaran GM, Guevara CA, Hajjar KA. 1994. An endothelial cell receptor for plasminogen/tissue plasminogen activator (t-PA) II. Annexin II-mediated enhancement
of t-PA-dependent plasminogen activation. J. Biol. Chem. 269:21198–203
137. Laplaud PM, Beaubatie L, Rall SC, et al. 1988. Lipoprotein(a) is the major apo B-containing lipoprotein in the plasma of a hibernator hedgehog (Erinaceus europaeus). J. Lipid Res. 29:1157–70