

Review

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Lipoprotein(a): from ancestral benefit to modern pathogen?

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Summary

We review current concepts regarding the genetic, structural and metabolic features of lipoprotein(a), a major inherited cardiovascular pathogen. Although lipoprotein(a) is almost completely confined to a subset of primates, the hedgehog produces a lipoprotein(a)-like complex, which appears to have evolved independently from that of humans. The physiological role of lipoprotein(a) in humans is still

unclear, and individuals with low or null concentrations of plasma lipoprotein(a) manifest no deficiency syndrome or disease. The integration of recent discoveries about the structure and metabolism of this unique lipoprotein particle has allowed the formulation of some hypotheses concerning the evolutionary advantages of synthesizing lipoprotein(a)-like particles.

Structure and metabolism of lipoprotein(a)

Lipoprotein(a) (Lp(a)) is a low-density lipoprotein (LDL)-like particle formed by the association of the highly polymorphic glycosylated apolipoprotein(a) (apo(a)) with apolipoprotein B100 (apo B100), the classic protein moiety of LDL.¹ In assembled Lp(a) lipoprotein particles, apo(a) is attached to apo B100 through a single disulphide link between apo B100 Cys 3734 and apo(a) kringle IV type 9 Cys67;² additional non-covalent interactions play accessory roles in promoting, mediating and reinforcing the association between the apolipoproteins.^{3,4} Under microscopic analysis of Lp(a) particles, apo(a) assumes a belt-like structure; both apo(a) ends are attached at two distant sites to a spherical LDL.⁵

Although apo(a) transcripts have recently been found in adrenal glands, lungs, pituitary, brain and testes,⁶ circulating apo(a) is mainly synthesized by the liver as a precursor with lower molecular mass

which is processed into the mature form and then secreted into the blood stream.⁷ Rapidly after secretion, free apo(a) binds to circulating LDLs to generate complete Lp(a) particles.⁸ The assembly of Lp(a) occurs almost exclusively extracellularly, as no apo(a)-apoB100 complexes can be detected within cells.⁷ From the composition and physicochemical properties of Lp(a-), the lipoprotein remnant derived after dissociation of apo(a) from Lp(a) by chemical reduction, Lp(a) can be reasonably considered a genetically-determined variant of LDL, increased in density and size (Table 1).⁹ Lp(a) belongs to the heterogeneous family of cholesterol-enriched lipoproteins: cholesterol, in either free or esterified form, represents almost 40% of its total mass. The relative weight of phospholipids (17–24%) is comparable to that of proteins (17–29%), whereas the triglyceride content is rather limited, usually below 9%.^{9–14}

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Table 1 Main physicochemical properties and composition of LDL, Lp(a) and Lp(a-)⁹⁻¹⁴

	LDL	Lp(a)	Lp(a-)
<i>Physicochemical properties</i>			
Molecular mass (Da)	$(2.9) \times 10^6$	$(3.8-4.0) \times 10^6$	$(3.2-3.3) \times 10^6$
Diameter (nm)	25.9 ± 0.1	28.3 ± 0.5	26.1 ± 0.1
Density (g/l)	1019-1063	1006-1125	1028
Half-life (days)	2-3	3-4	Unknown
<i>Composition (%)</i>			
Protein	26-31	17-29	24
Free cholesterol	9	6-9	9
Esterified cholesterol	40-43	35-46	40-41
Triglycerides	4-6	4-8	5-6
Phospholipids	20-22	17-24	20

Almost 23% of the apo(a) mass is attributable to N- and O-glycosides, producing the remarkable electro-negative potential of the Lp(a) lipoprotein particle.¹²

Aside from the structural homology to LDL, Lp(a) displays unique metabolic features. About 90% of Lp(a) concentration is under genetic regulation. The greatest part of the variability in Lp(a) levels (over 40%) is accounted for by quantitative polymorphism in the internal sequence of the apo(a) gene; qualitative polymorphisms in the sequence of the promoter play only a minor role (from 10 to 14%).¹⁵ Despite this genetic regulation, some metabolic abnormalities may have effects on Lp(a) levels in plasma.^{16,17} Among these, the acute-phase response, hormonal homeostasis, diabetes, liver and renal failure, and defects in the LDL-receptor gene have all been shown to influence the still enigmatic metabolism of this lipoprotein.

The apo(a) gene cluster

The ability to synthesize apo(a) is confined to a restricted group of primates; however, the insectivore hedgehog produces an apo(a)-like protein composed of multiple tandem repeats of a plasminogen kringle III homologous domain but lacking the protease domain.¹⁸ Apo(a) sequence comparisons and phylogenetic analysis indicate that human and hedgehog genes evolved independently from different sequences, providing a novel model of 'convergent' molecular evolution.¹⁹

The human apo(a) gene is located in a gene cluster within 400 kb of genomic DNA on the telomeric region of chromosome 6 (6q26-27),^{20,21} including the sequences encoding apo(a), plasminogen and other two pseudogenes with highly homologous untranslated 5' flanking regions.²² Hybridization analysis and reverse transcriptase polymerase chain reaction have identified three additional homologous genes designated as plasminogen-

related genes, unlinked to the apo(a) gene cluster and resident on chromosomes 2 and 4.²²

The apo(a) gene belongs to a puzzling gene family that includes several similar sequences encoding prothrombin, tissue-type plasminogen activator (t-PA), urokinase A-chain, plasminogen, coagulation factor XII, macrophage stimulating factor, hepatocyte growth factor and other proteins and polypeptides of unclear function.²³ Nucleotide analysis of human genes encoding these proteins reveals that sequences of exons and relative boundaries differ only from 1 to 5%, and that the types of exon/intron junctions and the positions of introns in the sequences are almost identical. These data suggest that the genes might have developed during recent primate evolution from a common ancestral component of the kringle-related serine proteases, most likely plasminogen, via duplication and exon shuffling.^{18,24} The apo(a) gene shares the highest homologies with the gene of the zymogen plasminogen; the sequence encoding for plasminogen kringle V domain is retained, whereas the plasminogen kringle IV domain encoding sequence exists in multiple variable tandem repeats. In contrast, apo(a) lacks the sequences of plasminogen preactive region and plasminogen kringle domains I through III. Despite the strong genetic homologies, a single point mutation in the sequence of the protease domain deprives apo(a) of most of plasminogen's enzymic properties. Sequencing of cloned human apo(a) complementary DNA revealed that apo(a) contains 10 different kringle IV subtypes, designed as types 1-10.²⁵ The high quantitative polymorphism in the sequence encoding the plasminogen kringle IV type 2 domain explains the high degree of individual allelic size polymorphism of the protein as, to date, no fewer than 34 size alleles have been identified in the apo(a) locus, encoding as many detectable isoforms in plasma.²⁶⁻²⁷ The size of the apo(a) particle usually determines its rate of hepatic synthesis and secretion; null alleles,

producing virtually no detectable circulating Lp(a), can be frequently observed. The molecular basis of these null alleles seems to be an in-frame 47-amino-acid deletion in the sequence of the protease domain that hinders the correct splicing of mRNA and generates a defective protein, irregularly subjected to a sequence of intracellular rearrangements which are essential for processing and secretion of complete and functional particles.²⁸ Among these, the trimming of N-linked glucoses, which occurs after the folding of the protein into the endoplasmic reticulum, is thought to be a critical process.²⁹

Little is known about the two adjacent apo(a)-related genes located on the apo(a) gene cluster on chromosome 6q26-27, called apo(a)-related genes C and B, respectively. Although apo(a)-related gene B appears to be substantially silent, a 132-amino-acid human liver transcript composed of a secretion signal and a single kringle domain from the apo(a)-related gene C was recently identified in plasma.²² It is not yet clear whether this truncated genomic product has any substantial biological function in humans.

The benefits of Lp(a)

As nothing seems to happen casually in nature, we should be able to identify at least one reasonable explanation for the appearance of Lp(a) in humans and hedgehogs. There are several different human proteins and polypeptides whose biological functions are yet unclear; however, it does not necessarily mean that they are useless. This might be particularly true for Lp(a).

Lp(a) promotes tissue repair

It now seems very likely that Lp(a) offered an evolutionary advantage to humans by promoting or accelerating the healing of wounds and the repair of tissue injuries and vascular lesions. This hypothesis is supported by several lines of biological evidence.

Lp(a) behaves as an acute-phase reactant. The sequence of the apo(a) gene contains several interleukin 6 (IL-6)-responsive elements that enhance transcription of the gene.³¹ IL-6 generates a marked, dose-dependent enhancement of apo(a) mRNA synthesis that leads to the accumulation of Lp(a) particles in hepatocyte culture,³² and several prospective clinical trials demonstrated significant rises in plasma Lp(a) after inducing different forms of acute phase response *in vivo*.³³

Due to the additional presence of apo(a), Lp(a) can be recognized by a broad variety of receptors at the surface of endothelial cells, macrophages, fibroblasts and platelets.^{34,35} Defensin, a peptide

released from activated or senescent neutrophils, enhances the binding of Lp(a) to endothelial cells by approximately four-fold and to smooth muscle cells by six-fold.³⁶ Although it is not yet clear whether Lp(a) particles are internalized directly or instead by prior extracellular degradation, the large amount of cholesterol carried by the lipoprotein can easily be extracted and used at the site of its accumulation.

Lp(a) binds to several components of the vascular wall and of the sub-endothelial matrix;³⁷ this binding is partially mediated by the lysine binding sites (LBS) of its apo(a) moiety.³⁵ High affinity bindings to fibronectin, fibrinogen, glycosaminoglycans and proteoglycans were observed in the presence of Ca^{2+} and Mg^{2+} ions; further weaker interactions were described with laminin and beta-2 glycoprotein I, but no binding was observed to von Willebrand factor, vitronectin or collagen type IV.³⁷⁻³⁹

Lp(a) inhibits fibrinolysis

Lp(a) displays unequivocal growth-factor-like properties, promoting the growth of human umbilical vein endothelial cells (hUVECs) in synergy with basic fibroblast growth factor and insulin,⁴⁰ and enhancing the proliferation of human vascular smooth cells (hVSMCs) in culture by inhibiting the activation of transforming growth factor- β .⁴¹ These observations are unsurprising, considering that apo(a) belongs to a family of growth factors evolved from a common ancestral kringle-containing serine protease, including the hepatocyte growth factor/scatter factor (HGF/SF), a potent effector in promoting growth, movement, and differentiation of epithelia and endothelia, and the hepatocyte growth-factor-like/macrophage-stimulating protein (HGF1/MSP), an effector of macrophage chemotaxis and phagocytosis.⁴²

A conceivable scenario is summarized in Figure 1. As a vascular injury occurs, the acute-phase response, concomitantly induced by the cellular release of several mediators, including IL-6, stimulates the hepatic synthesis of newly-formed apo(a) molecules, thereby producing complete circulating Lp(a) particles in the blood stream. Shortly afterwards, Lp(a) accumulates at the site of the vascular injury as it binds to cellular receptors at the surface of residual vascular cells, macrophages and platelets, to the exposed sub-endothelial matrix and to immobilized fibrin. The large amount of apo(a) bound to the fibrin surface and, to a lesser extent, to platelets and endothelial cells, inhibits the lysis of the clot. At the same time, the growth-factor-like properties of Lp(a) promote vascular repair, and cell regeneration is ensured by the large amount of cholesterol carried by the lipoprotein. In contrast to other cholesterol-rich lipoproteins, Lp(a) concentration is not substantially influenced by changes in dietary

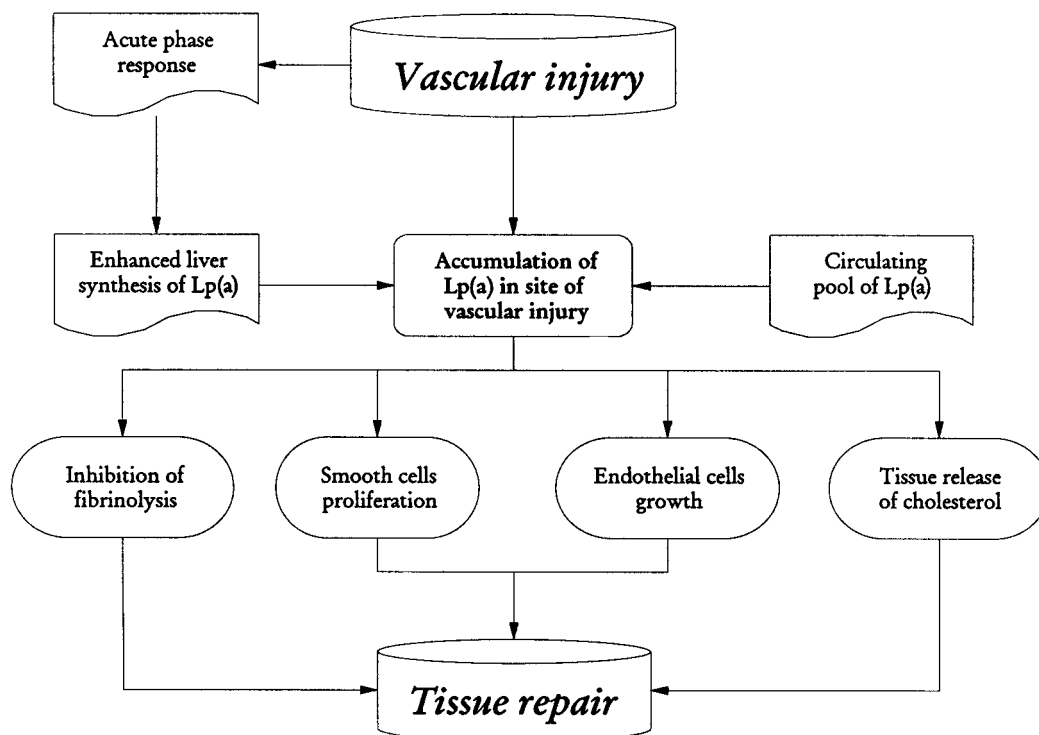


Figure 1. The role of Lp(a) in tissue repair.

habits. Therefore, it is conceivable that, given the different dietary habits of primates several million years ago, and the much lower plasma levels of total cholesterol and LDL-cholesterol, the amount of cholesterol carried by Lp(a) might have represented an important source of substrates for cell regeneration and growth. On this basis, Lp(a) could have been an essential component for tissue repair, whose primary functions might have been the delivery of large amount of cholesterol to peripheral cells and the promotion of regeneration following events such as injuries or inflammatory processes. Convincing support for this hypothesis was recently provided by Yano and colleagues, who described a markedly positive staining for Lp(a) closer to the surface of the fibrous cap, as well as in endothelial cells, and in the extracellular space of small vessels underlying the fibrous cap of granulation tissues during wound healing.⁴³

Lp(a) inhibits cancer growth and spread

O'Reilly and colleagues recently demonstrated that angiostatin, a 38 kDa fragment generated by cancer-mediated proteolysis of plasminogen, including plasminogen kringle domains I through IV, inhibits neovascularization of tumours and metastasis.^{44,45} Furthermore, a recombinant form of plasminogen kringle V domain, sharing high sequence homology with the four kringles of angiostatin, inhibits endothelial cell migration.⁴⁶

As most plasminogen-derived kringles have a strong inhibitory effect on angiogenesis^{45,46} and apo(a) kringle domains are highly homologous to plasminogen residues (77–100%),²⁵ it is quite conceivable that Lp(a) kringle fragments produced after physiological degradation of whole particles *in vivo*⁴⁷ have similar properties in antagonizing or reducing growth and spread of cancers. However, the clinical relationship between Lp(a) and cancer is still rather obscure. The concentration of Lp(a) is commonly reported to be significantly increased in cancer patients as compared to healthy controls, irrespective of source and degree of malignancy of the tumour.⁴⁸

Taken together, this evidence might ascribe an essential role to Lp(a) in the biological fight against malignancy. Among its various responses to cancer, the organism might generate a substantial rise in Lp(a) concentrations, and the large content in kringle domains of apo(a) might then exert a powerful anti-neoplastic effect. Although this hypothesis sounds very attractive, there are some serious difficulties. First, the recognized growth-factor-like functions of Lp(a) on endothelial and smooth cells appear somewhat incompatible with an eventual inhibitory effect on angiogenesis; secondly, systemic administration of intact kringle-containing proteins does not inhibit neovascularization and growth of metastases and primary tumours⁴⁶ and, to our knowledge, no study has yet investigated the hypothetical anti-neoplastic function of Lp(a) *in vitro*; finally, the current clinical

observations require further support as they emerged substantially from longitudinal studies—no definitive prospective investigations are available at present.

Lp(a) is a surrogate for ascorbate

According to the classic 'unified theory' of former Nobel prize-winner Linus C. Pauling and Mathias Rath, human occlusive cardiovascular disease is a degenerative condition induced by chronic ascorbate (vitamin C) deficiency, in which the large extracellular deposition of Lp(a) represents a powerful biological defensive mechanism^{49,50} Thereby, Lp(a) is regarded as a surrogate for ascorbate. Some evidence has been found to support this hypothesis.

First, the original identification of Lp(a)-immunoreactive material was restricted to primates and to the guinea pig, both of which have lost their ability to synthesize vitamin C *de novo*.⁴⁹ On this basis, Lp(a) might have replaced ascorbate in most species as a result of the evolutionary process.⁵⁰ The biological capability to synthesize ascorbate was probably lost in primates and guinea pigs after the introduction of substantial changes in dietary habits, presumably towards foods containing larger amount of vitamin C.

Secondly, adequate amounts of ascorbate (40 mg/kg body weight/day) prevent the accumulation of Lp(a) in the arterial wall and the consecutive development of atherosclerosis in animal models.⁵¹

Thirdly, Lp(a) might share some basic properties with ascorbate. It was suggested that Lp(a) contributes to the strengthening of the extracellular matrix, particularly in circumstances of ascorbate deficiency. At lower ascorbate concentrations, the instability of the extracellular matrix resulting from impaired synthesis of collagen and elastin might be temporarily improved by a large deposition of Lp(a). Moreover, Lp(a) may delay lipid peroxidation.^{49,50} Finally, elevated concentrations of plasma Lp(a) are usually associated with cardiovascular diseases, where the overall incidence could be decreased by dietary supplementation with ascorbate.⁵⁰ Similar observations have also been made in cancer and diabetes patients.

To our knowledge, no other reliable clinical or biological evidence regarding strong relationships between Lp(a) and ascorbate in humans has been published after the studies of Rath and Pauling. Additionally, further studies failed to demonstrate either Lp(a)-immunoreactive material in plasma or apo(a) mRNA in the liver of the guinea pig, suggesting that the material originally identified by Rath and Pauling might be cross-reacting proteins or polypeptides.¹⁹ Finally, high-dose ascorbate supplementation in patients with premature coronary heart disease did not produce any clinically important lowering

effect on plasma Lp(a).⁵² Taken together, this evidence suggests that, although vitamin C might represent a powerful agent against heart disease, its biological relationship with Lp(a) needs further investigation.

The pathogenicity of Lp(a)

Lp(a) and atherosclerosis

Shortly after its discovery, raised levels of Lp(a) were repeatedly associated with an increased incidence of a variety of cardiovascular diseases, including silent coronary artery disease (CAD), acute myocardial infarction (AMI), asymptomatic carotid atherosclerosis, stroke, and peripheral artery occlusive disease (PAOD).^{53,54} Additionally, elevated Lp(a) levels in plasma were shown to be strong indicators of vasculogenic erectile dysfunction⁵⁵ and retinal artery occlusion.⁵⁶ Usually, the Lp(a) familial excess represents the most frequent lipoprotein abnormality observed in patients with premature myocardial infarction.⁵⁷ Although retrospective case-control studies basically agreed in ascribing a substantial role to Lp(a) in the pathogenesis of cardiovascular diseases, this association emerged less clearly from prospective studies. In fact, whereas some prospective studies reported raised levels of Lp(a) in patients with CAD,^{58–64} others failed to demonstrate such an association.^{65–67} Several explanations were proposed for this apparent contradiction. Briefly, due to the intrinsic genetic, structural and metabolic complexity of Lp(a), reliable conclusions drawn from the analysis of results of Lp(a) investigations require the unconditional application of rigorous and standardized protocols.^{53–54,68} Furthermore, emerging evidence demonstrates that the atherogenic properties of Lp(a) are intimately linked to those of LDL;⁶⁹ accordingly, the cardiovascular potential of Lp(a) appears more substantial in hypercholesterolaemic subjects,⁷⁰ and substantial reductions in LDL-cholesterol (LDL-C) attenuate the clinical threat of persistent elevations of Lp(a).⁷¹ From this perspective, although common treatments for lowering LDL-C usually have no effect on Lp(a), the identification of patients with raised concentrations of both Lp(a) and LDL-C might be crucial in clinical management, basically promoting a more aggressive treatment of other concurrent modifiable risk factors. Some doubts remain about the atherogenic potential of Lp(a) in Black populations. In fact, although the concentration of Lp(a) in African Americans is from two- to four-fold higher than in matched Caucasian Americans, the overall atherogenic risk in the two racial groups appears comparable.

Several lines of biological evidence can be used

to explain the role of Lp(a) in the genesis, development and complication of atherosclerotic lesions. Lp(a) immunoreactive material can be selectively demonstrated in the vascular wall of several arterial vessels, including the aorta⁷², and coronary,⁷³ cerebral⁷⁴ and peripheral arteries⁷⁵; in those sites, the relative amount of apo(a) deposition is significantly related to the extent of atherosclerosis.⁷⁴ Accordingly, large amounts of Lp(a) can be demonstrated in growing atherosclerotic plaques and vein grafts.⁷⁶ In growing atherosclerotic lesions, the accumulation of apo(a) in degraded, free and intact (but oxidized) forms appears to be preferential to that of other apolipoproteins.⁷⁷ The cellular uptake and degradation of Lp(a) follows several pathways, as Lp(a) particles bind to a wide variety of cellular receptors^{78–84} and other unrecognized endosomal membrane proteins.⁸⁰ Lipoprotein lipase enhances the cell association of Lp(a) five-fold and the consequent cellular degradation by about threefold,⁸⁵ whereas the oxidative modification of Lp(a) results in avid uptake by monocyte-macrophages.⁸⁶ The affinity of Lp(a) to triglyceride-rich lipoproteins and LDLs, and the strong molecular interactions with several components of the endothelial matrix might further enhance the catabolism of Lp(a) by alternative, as yet unclear pathways, promoting accelerated internalization and degradation of cholesterol-rich lipoproteins.⁸⁷ Recently, several biological studies demonstrated that Lp(a): (i) displays various growth factor-like properties for several vascular cells *in vitro*;^{40,41} (ii) triggers chemotaxis in human monocytes;^{88,89} and (iii) enhances the expression of intercellular adhesion molecule (ICAM)-1 in cultured hUVECs.⁹⁰ Finally, increased Lp(a) levels are associated with a selective impairment of vasodilator capacity of receptor-mediated endothelial stimuli, contributing to the pathogenesis of myocardial ischaemia.⁹¹

Lp(a) and thrombosis

Raised Lp(a) concentrations have been observed in patients with several thrombotic occlusive disorders such as pulmonary embolism,⁹² central retinal vein occlusion⁹³ and interference in placental circulation causing fetal growth retardation.^{94,95} Lp(a) levels are strong predictors of both occlusive events following vascular and endovascular surgical procedures⁹⁶ and development of thrombotic episodes in patients with severe rheumatological diseases.⁹⁷ Finally, the convergence of the strong atherogenic and thrombotic potentials of Lp(a) plays a pivotal role in the complication of atherosclerotic lesions, as usually occurs after rupture or ulceration of atherosclerotic plaques.⁹⁸

Several plausible mechanisms were proposed to

explain the anti-fibrinolytic potential of Lp(a).⁹⁹ A considerable part of the anti-fibrinolytic properties of apo(a) seems to reside in its molecular similarity to plasminogen.²⁵ Lp(a) inhibits plasminogen binding and activation at the surface of stabilized fibrin, endothelial cells and platelets in a dose-dependent fashion, and the inhibitory effect on plasmin generation *in vitro* may be related to the size of the apo(a) particle, as smaller isoforms produce more pronounced inhibition.¹⁰⁰ Recently, Harpel and colleagues demonstrated that the strength of the binding between apo(a) and stabilized fibrin can be increased by incubation with homocysteine and other sulfhydryl compounds, such as cysteine, glutathione and N-acetylcysteine.¹⁰¹ This latter observation is particularly attractive as it might provide a reliable synergy between Lp(a) and homocysteine in the intricate genesis of thrombotic disorders. Sangrar and colleagues provided further insights into the inhibitory effects of Lp(a) on plasmin generation, demonstrating that a recombinant form of apo(a) inhibits plasminogen binding to plasmin-modified fibrinogen surfaces.¹⁰² Additional studies demonstrated that: (i) Lp(a), especially in oxidized form, increases over two-fold the endothelial synthesis and secretion of PAI-1 *in vitro*, especially for the 2/2 PAI-1 genotype;^{103,104} (ii) Lp(a) inhibits the secretion of t-PA from human endothelial cells;¹⁰⁵ and (iii) t-PA binds reversibly to surface-bound Lp(a) inhibiting the tPA-mediated activation of Glu-PLG.^{102,106} The recently observed interaction between recombinant apo(a) and beta2-glycoprotein I³⁹ raises new speculations about the active participation of Lp(a) in thrombotic and autoimmune processes, and deserves further in-depth investigation.

Conclusions

Only few animal species have developed the ability to synthesize Lp(a) along their evolution: a subset of primates and the insectivore hedgehog. According to a recent theory, the phylogenetic evolution of the hedgehog apo(a)-like gene can be dated back to about 80m years ago, whereas the appearance of apo(a) in primates occurred much more recently, probably during the recent evolution of these species.¹⁸ Additionally, the hedgehog apo(a)-like gene shows substantial distinctive features in terms of structure and evolutionary history from human apo(a); in fact the former gene encodes a protein composed of highly repeated copies of a plasminogen kringle III-like domain but is completely lacking the sequences encoding the plasminogen preactivation peptide, for plasminogen kringles I, II, IV and V and for the protease domain.¹⁸ It is well known that the restricted availability of biological substrates and

the necessary adaptation to particular habits or habitats has produced widespread phenomenon of molecular convergence in nature.^{107,108} As a common ancestry can be excluded, the appearance of Lp(a) in such two widely divergent groups of species represents one of the most convincing examples of convergent molecular evolution towards a common potential benefit.

Similarly to other kringle-containing proteins and polypeptides originated from a common ancestral gene, apo(a) is composed of various functional domains and thereby represents a typical example of the so-called 'mosaic proteins'.¹⁰⁹ So far, the tissue repair theory appears the most convincing of the various hypotheses concerning the original function of Lp(a) *in vivo*.⁴³ However, as the expression of hepatic and extrahepatic apo(a) are reported to be subject to separate control mechanisms, liver-produced apo(a) might exert different functions from apo(a) produced in other tissues.⁶

At present, we have strong evidence that the original biological role of this unique and elusive lipoprotein has disappeared, gradually obscured by its adverse and pathological effects. The high degree of polymorphism in the apo(a) gene, the over 1000-fold range of variation of Lp(a) levels between individuals,²⁶ the highly skewed distribution towards lower concentrations in Caucasian populations and the observation that subjects with undetectable Lp(a) levels in blood manifest no apparent deficiency syndrome, confine Lp(a) to the role of a genetically determined cardiovascular pathogen in search of a new positive role.^{110,111} Unfortunately, several biological properties that might be the basis for useful activities also represent key mechanisms of the atherogenic and thrombogenic potential shown by Lp(a). It is quite possible that a considerable part of the modern pathological effects of this enigmatic lipoprotein represents nothing more than vestiges of its ancestral useful properties.

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