Lipoprotein(a) in Vascular Disease, Cancer and Longevity

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Lipoprotein(a) [Lp(a)] is a unique lipoprotein with controversial functions. Lp(a) contains apolipoprotein(a) [apo(a)] covalently attached to apolipoprotein B on the low-density lipoprotein (LDL) particle. The distribution of blood Lp(a) concentrations in several populations have been found to be skewed with Lp(a) being mostly present at low level (0 – 200 mg/L). A high Lp(a) concentration (greater than 200 mg/L) in blood increases the risk of various vascular diseases including chronic heart disease, acute myocardial infarction and cerebral thrombosis. With Lp(a) potentially having such deleterious effects, there is a need to ask what are the evolutionary benefit(s) of Lp(a) to humans and other mammals that have it. Lp(a) has been reported to offer a number of benefits such as providing protection from LDL cholesterol and providing a source of cholesterol in wound tissue. Furthermore, some evidence is emerging that Lp(a) has anti-tumor properties. Other surveys have indicated that Lp(a) is advantageous because it promotes longevity. Lp(a) is only found in humans, old world monkeys and hedgehogs. Individuals who do not express Lp(a) do not show any disease symptoms, which indicates that Lp(a) is not essential for human life. It still remains unclear why mysterious Lp(a) has evolved and is present in humans. *(Chang Gung Med J 2011;34:555-64)*

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Lipoprotein(a) [Lp(a)] is a variant form of low-density lipoprotein (LDL) and was discovered in 1963 by Berg in rabbits immunized with human LDL.[1] In addition to producing antibodies against LDL, the rabbits also produced an antibody against a variant form of LDL that was later named Lp(a). Lp(a) is an LDL particle with apolipoprotein(a) [apo(a)] protein attached loosely to the surface by a disulfide bond linked to the only protein on LDL particle, namely apolipoprotein B (apoB). Blood levels of Lp(a) in human populations range from undetectable, to greater than 1000 mg/L with the normal range being less than 200 mg/L. LDL cholesterol is considered as 'bad cholesterol' since too high level of this cholesterol is associated with an increased risk of coronary artery disease and stroke. The same hazard is associated with elevated blood Lp(a) levels. Lp(a) is only found in humans, old world monkeys and hedgehogs and is not found in other animals. It is not clear why the apo(a) gene evolved and why it is maintained in such a limited range of species. In this review, the good and bad aspects of

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Lp(a) are discussed with regard to its association with vascular diseases, anti-tumor properties and longevity.

Genetics of apolipoprotein(a) and assembly of lipoprotein(a)

Apo(a) was first sequenced on a gene obtained from a patient with 37 kringle IV (KIV) repeats. The apo(a) mRNA was 14 kilobase (kb) and contained 4529 amino acids (aa) with a 19aa signal sequence.[2] This gene is highly homologous to plasminogen (pmg). The pmg gene has one each of the kringle (K) sequences KI, KII, KIII, KIV and KV together with a protease domain. The apo(a) gene includes the pmg gene KIV domain from five to fifty times and skips KI, KII and KIII,[3] so creating a very polymorphic apo(a) protein that can range in molecular weight from 200 kilodalton (bp) to 800 kDa. Each KIV repeat is 342 basepair (sp) long and encodes 114aa. There is one intron inside each kringle and one intron between each pair of kringles; the break point for each intron is identical to that found in the pmg gene. Each kringle is shaped by three disulfide bonds that are Cys1-6, Cys2-4 and Cys3-5 pairs (Fig. 1). The kringle IV repeats of the apo(a) protein are divided into ten different types that differ in their aa sequences. Among them, kringle IV type 2 exhibits variable repeat numbers. The kringle type 2 is subdivided into type 2A and type 2B according to DNA sequence differences, although their protein sequences are identical (Fig. 2).[2] Apo(a) also contains KV and protease domains. A mutation (Arg to Ser) in the protease domain renders apo(a) unable to perform its self-cleavage protease function.

Apo(a) and pmg genes are linked together and found on human chromosome 6q26-27.[4] Each individual contains two alleles of the apo(a) gene and the two alleles may be different in size. The combined expression of both alleles determines an individual's plasma Lp(a) level. The apo(a) structure is mostly random and is covalently attached to the apoB Cys3734 residue. The apo(a) Cys4057 residue that binds to apoB is within the KIV type 9 of apo(a).[5] The interaction of apo(a) with LDL involves several non-covalent lysine binding sites, these are apo(a) KIV type 6-8 and apoB Lys680 – Lys690,[6,7] the result is that the apo(a) protein winds around the LDL particle. After treatment with a lysine analog, 6-aminohexanoic acid that competes with lysine binding sites,[8] or after strong shearing in the blood,[9] the apo(a) protein undergoes a conformation change and extends out, remaining linked to the LDL particle by the disulfide bond (Fig. 3).

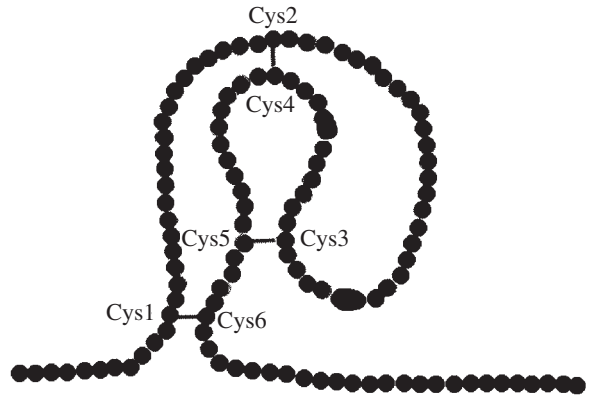


Fig 1. Typical kringle structure of apo(a) KIV. The shape is maintained by three pairs of cysteine disulfide bonds.

Blood Lp(a) level is determined by the rate of apo(a) synthesis.[10] The regulation of apo(a) protein expression is determined at both the transcription and post-translational stages. The promoter activity of individuals with Lp(a) levels greater than 400 mg/L show no correlation with the regulation of apo(a) gene transcription,[11] However, comparisons between the promoters from individuals with Lp(a) levels less than 50 mg/mL and those with Lp(a) lev-

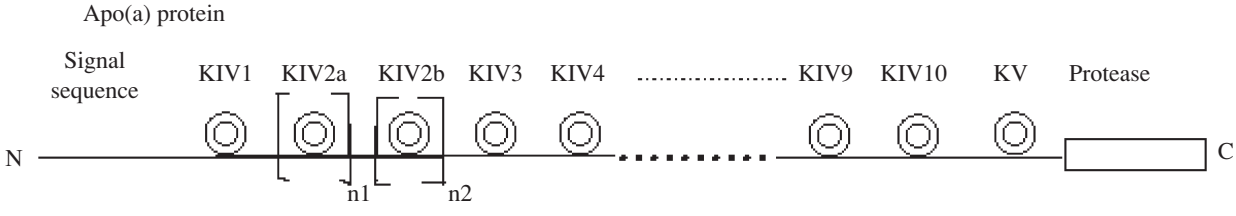


Fig 2. The structure of the apo(a) protein. Each double circle represents a kringle. There are variable numbers of KIV together with one KV and a protease domain. The variation primarily occurs in the number of KIV2a and KIV2b sequences.

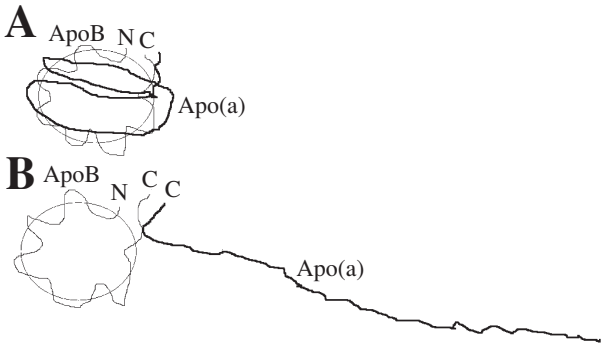


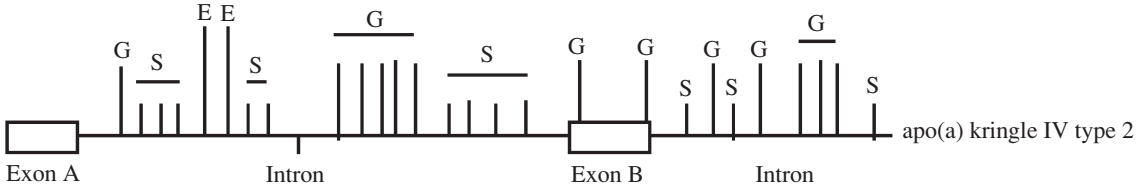
Fig 3. The closed and extended form of Lp(a). (A) Under normal condition, Lp(a) surrounds the LDL particle on the surface. (B) In case of lysine analogue treatment or under high shear condition, apo(a) extends and hangs loosely from the LDL although still attached by a single disulfide bond.

els greater than 300 mg/mL do show that a high Lp(a) level is correlated with high promoter activity,[12] and that high Lp(a) levels usually correlate with one high-promoter-activity allele and one low-promoter-activity allele.[13] This indicates that the Lp(a) levels are mostly affected by the dominant high-expression allele. Other enhancer and silencer sequences in the introns, both inside and between kringles, also have the ability to fine tuning transcription efficiency (Fig. 4). The apo(a) gene promoter has a number of IL-6 binding sites that characterize the apo(a) protein as an acute phase protein. Several polymorphisms in the apo(a) genes, such as –821 G/A, –1373 pentanucleotide (TTTTA) repeats and –868 T repeats have been associated with increased plasma Lp(a) levels.[11,13]

Regulation of apo(a) expression is also affected at the post-translational level. Apo(a) protein is highly glycosylated and contains 30% – 50% carbohydrate. Apo(a) has N-glycosylation sites in the kringle region and O-glycosylation sites in the inter-chain regions connecting the kringles. Glycosylation is required for the secretion of apo(a). The secreted apo(a) is assembled with apoB on LDL outside of the cell in circulation[14] and the post-translational modification greatly affects the secretion of apo(a) protein and the Lp(a) concentration. Any defect in the splice junction,[15] in the protein folding due to mutations in the kringle region, or in sugar processing during protein transport from ER to the Golgi apparatus may result in degradation of the apo(a) protein.[16] This may explain why it is that individuals having Lp(a) with a high number of KIV repeats may exhibits low Lp(a) concentrations and also rationalizes the null allele phenotype.[17,18]

Since the model experimental animal mouse does not possess the apo(a) gene, transgenic mice expressing the human apo(a) gene were created; the transgenic mice produced free apo(a) in blood and are prone to atherosclerosis when fed a high fat diet.[19] Human apo(a) was found to conjugate poorly with mouse apoB. Transgenic mice expressing both human apoB and apo(a) proteins were created and Lp(a) was then found in triglyceride-rich particles.[20] This finding was in agreement with a previous report showing that Lp(a) is associated with triglyceride-rich chylomicron (d < 1.006 g/mL),[21] although Lp(a) is considered to be present in a density range of 1.05 – 1.12 g/mL. Lecithin cholesterol acyl transferase (LCAT) is an enzyme that catalyzes the formation of cholesterol ester. Patients lacking LCAT do not form Lp(a), indicating that LCAT activity is required for LDL complex formation with apo(a),[22] although the mechanism is unclear.

In conclusion, Lp(a) seems to be nonessential in



S: SFA 5' GGA GCA GGA 3'
G: GCF 5' GCGGGGC 3'
E: SV 40 core enhancer (SV40E) 5' GTG G(A/T) (A/T) (A/T)G 3'

Fig 4. Multiple enhancer (E) and silencer (SFA, S and GCF, G) sequence homologs are found in the apo(a) introns within the kringles and between the pairs of kringles. The exon of each kringle is divided into exon A and exon B.

humans, since individuals who do not have Lp(a) in their blood do not seem to suffer any ill effects. Blood levels of Lp(a) are controlled by the apo(a) synthesis rate, which is in turn controlled by a very complex system, including kringle repeat number, various genetic polymorphisms that control transcription efficiency, mRNA stability, translation efficiency, protein folding and post-translational glycosylation.

Lp(a) and vascular disease

Lp(a) exhibits a skewed concentration profile in various populations with the majority having it present at low levels (larger isoform), while in the disease group, the curve distribution shifts to high concentrations. For the African-American population, the distribution of Lp(a) level in normal groups is shifted to a high concentration (medium isoform).[23] Elevated plasma Lp(a) levels have been reported to be an independent risk factor for coronary heart disease and stroke.[24-27] The risk seems to depend on racial differences with the risk being present for Caucasians, Japanese and Chinese, but not for African-Americans.[28] Earlier prospective studies found no association between Lp(a) level and the risk of myocardial infarction,[29,30] although later studies and further analyses have suggested a positive correlation.[31,32] In a survey of 68 coronary artery disease (CAD) patients, a small sized apo(a) allele was identified as an independent risk factor.[33]

The pathology of Lp(a) is related to the properties of Lp(a) and apo(a). Although apo(a) is unable to self-cleave into an active protease, as occurs with pmg, it can bind and cleave fibronectin.[34] Lp(a) has been shown to react with glycosaminoglycan,[35] fibrin,[36] platelets,[37] β_2-glycoprotein I in human plasma[38] and magelin/glycoprotein 330 (gp330) in the kidney.[39] Lp(a) increases fibrin lysis time in stroke patients;[40] clots were found to be less porous and less susceptible to clot lysis.[41]

Lp(a) inhibits tissue plasminogen activator activation,[42] and competes with pmg for pmg receptors and annexin II co-receptors on the endothelial surface.[43,44] Elevated Lp(a) levels bind with annexin V (or annexin A5) and interfere with the shielding effect of annexin V on procoagulant phosphatidyl serine in the event of endothelial injury by inflammation;[45] both apo(a) and Lp(a) have been found to bind annexin V. The effect of Lp(a) on vascular pathology has been shown by its inhibition of TGFβ activity and increases in human vascular smooth muscle cell proliferation.[46,47] Elevated Lp(a) levels have also been reported to increase the risk of retinal vein occlusion and childhood arterial ischemic stroke.[48,49] Defensin, a small cationic cysteine-rich anti-microbial peptide[50] released from neutrophils, enhances Lp(a) binding to vascular endothelial and smooth muscle cells.[51] A number of therapeutic agents have been used to try and lower blood Lp(a) levels. Many lipid-lowering drugs are ineffective; however niacin and aspirin are effective. Niacin causes a flushing side effect and reduces triglyceride lipolysis, thus lowering Lp(a) levels.[52] Inflammation is closely associated with vascular diseases and in this context proinflammatory cytokine IL-6 enhances the apo(a) promoter and aspirin reduces apo(a) production transcriptionally.[53]

Interestingly, Mora *et al*. in a prospective survey of type 2 diabetes risks involving 26,746 women over a 13 year period, found that plasma Lp(a) level are negatively associated with type 2 diabetes mellitus.[54] Diabetic patients displayed high triglyceride levels and an inverse relationship between triglyceride level and Lp(a) concentration has been documented.[55] Lp(a) has also been considered to be a protective particle since the bulk of glycosylated apo(a) shields LDL. Normal Lp(a) levels provide an anticoagulation function[56] because Lp(a) inhibits platelet aggregation and decreases serotonin release and thrombaxane B_2 synthesis. The involvement of Lp(a) in anti-tumor formation/metastasis and longevity has increased interest in this lipoprotein, which is discussed further below.

Lp(a) and cancer

Cancers cause high death rates in humans. The association of Lp(a) with some cancers has been documented. Patients with different cancer types showed variations in Lp(a) levels. Elevated Lp(a) concentrations have been observed in breast[57] and lung cancers,[58] but Lp(a) levels are decreased in liver cancer.[59] As the liver is the major site of apo(a) synthesis, liver cancer is thought to affect the expression of apo(a) protein.

Cancer tissues receive a rich blood supply and inhibition of angiogenesis has been considered as one of the therapeutic strategies for cancer. An early study showed that removal of a primary tumor from

a cancer patient accelerates cancer growth at the metastatic site and a hypothesis was formed whereby primary tumors produce angiostatic factors that inhibit the growth of itself and metastatic tumors.[60] Angiostatin and endostatin[61,62] are two such molecules and their production is not encoded by novel genes, but by cleavage of kringle-containing proteins.[63] Kringle sequences are present in several molecules related to coagulation system. Plasminogen has kringle I, II, III, IV and V sequences, while prothrombin and tissue-plasminogen activator have kringle I and II sequences. Factor XII and uroplasminogen activator each contain a single kringle sequence. None of these molecules contains the large number of kringle IV repeats that apo(a) does. Degradation of the apo(a) component of Lp(a) is able to produce proteins of various sizes and containing different numbers of kringle IV repeats; as a consequence of this, the catabolic pathway of Lp(a) has become an area of interest.

As mentioned earlier, Lp(a) may be present at a density slightly higher than that of LDL, Lp(a) can also appear in the chylomicron/VLDL fraction. The Lp(a) catabolic pathway has been found not to involve the LDL receptor;[64] however, the VLDL receptor has been shown to take up Lp(a) by endocytosis and this interaction is mediated by apo(a).[65] Apo(a) is degraded to fragments of around 35 to 160 kDa and excreted in urine.[66] Kidney is suspected to be the main site for Lp(a) catabolism and the site for apo(a) fragmentation.[67,68] Apo(a) degradation products are found in urine and these fragments inhibited tube formation in human vascular endothelial cells.[69]

Further investigations have found that Lp(a) can be taken up by liver, kidney and spleen.[70] In the liver, Lp(a) uptake is inhibited by apo(a) suggesting that liver uptake of Lp(a) is mediated by apo(a).[71] Degradation of Lp(a) and formation of apo(a) fragments occur in skeletal muscle and various organs.[72] Regardless of the apo(a) allele size, fragments containing up to 6 KIV have been found to be excreted in urine. The enzymes responsible for Lp(a) degradation are metalloproteinases located in various tissues and organs. The cleavage of apo(a) is inhibited by EDTA, but not by aprotinin or leupeptin.

Animal studies have shown that tumor cells transfected with apo(a) kringle sequences give rise to tumors of reduced size. Expression of a cDNA fragment containing apo(a) KIV-9, KIV-10 and KV in the colorectal cancer cell line CT26 was shown to inhibit liver metastasis in BALB/c mice.[73] Even apo(a) kringle V alone expressed as soluble protein inhibits endothelial cell migration.[74] Apo(a) transgenic mice displayed reduced angiogenesis when injected with Lewis lung carcinoma cells as well as a lower microvessel density *in vivo*.[75] The anti-angiogenic activity effect on endothelial remodeling is thought to follow the order KV > KI > KIII > KII > KIV.[76]

Not withstanding the above findings, angiogenesis is required for wound repair and endothelial regeneration.[77] Yano et al. reported that Lp(a) assists wound healing by accumulating in healing tissue and Lp(a) also stimulates human umbilical vein endothelial cell migration and proliferation.[78] Additionally, Ribatti et al. reported Lp(a) enhances chick embryo chorioallantoic membrane angiogenesis.[79] Whether these angiogenic stimulation effects are related to atherosclerosis is unknown. In summary, kringles produced by apo(a) degradation display anti-angiogenesis and anti-tumor properties, while Lp(a) facilitates wound healing, possesses endothelial repair activity in relation to injured endothelium and promotes angiogenesis.

Lp(a) and longevity

The association of Lp(a) with vascular disease seems incompatible with longevity, whereas the anti-angiogenic and anti-neoplasm activities of the apo(a) degradation products favor survival. Oxidative stress is a marker of aging and oxidized lipoproteins are associated with vascular disease.[80] High anti-oxidant capacity favors a disease-free state and may contribute to longevity. High blood Lp(a) levels easily produce oxidized particles that are very atherogenic and Lp(a) with small apo(a) isoforms correlates with higher blood concentrations than apo(a) with larger isoforms.[81] Oxidized Lp(a) appears as small dense particles as shown by electron microscopy.[9]

It is therefore reasonable to assume that individuals with small Lp(a) isoforms and high Lp(a) levels are not in a favorable situation for survival. Yet reports of French centenarians (n = 109, mean age 101.5 $\pm$ 2.4 years old) who have high Lp(a) levels and small apo(a) isoforms suggests that there is an association of these forms with longevity.[82] Others have also reported that high Lp(a) levels are found more frequently in centenarians,[83] however this

trend does not seem to be present in the Japanese population.[84] Perhaps differences in races, living style and genetic buffering systems[85] all play important roles in longevity. Frequent physical activity generates sheer in blood flow and helps apo(a) to extend from the Lp(a) particle and this may facilitates the enzyme degradation of apo(a) protein to generate kringle-containing degradation products with anti-cancer properties. Such a process might contribute to longevity.

Conclusion

Elevated Lp(a) levels are associated with coronary artery diseases and ischemic stroke. Lack of Lp(a) does not produce deleterious effects in humans. Whether the pathological effects of Lp(a) on vascular disease are only associated with the oxidation of LDL particles remains an open question. Apo(a) is highly glycosylated and can attach to several different extracellular matrix components, thus it may contribute to vascular diseases. However Lp(a) is also involved in tissue repair and may have an effect in shielding from LDL cholesterol. Therefore Lp(a) could be beneficial to humans in wound repair, although it is not known whether this effect is associated with the affinity of apo(a) for extracellular matrix components. Degradation products of apo(a) are anti-angiogenic and exhibit an anti-tumor effect. In this aspect, Lp(a)/apo(a) may be beneficial to humans and it is therefore not surprising to find that Lp(a) is related to longevity, A summary diagram of the Lp(a)/apo(a) relationship to their pathophysiological functions is presented in Fig. 5. The balance between the beneficial and adverse roles of Lp(a)/apo(a) remains a subject for future investigation.

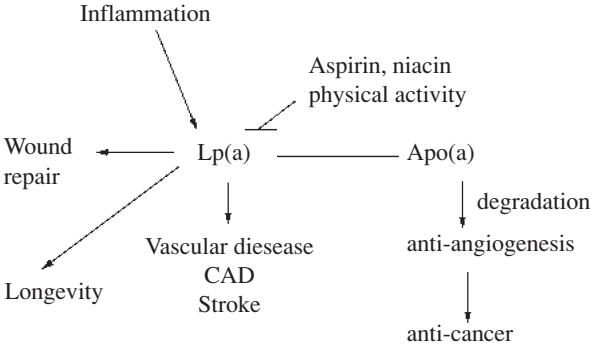


Fig 5. Summary of the association of Lp(a) and apo(a) with vascular diseases, wound repair, longevity and anticancer properties. Inflammation increases Lp(a) level, while aspirin, niacin and physical activity decrease Lp(a) levels.

Acknowledgements

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脂肪蛋白(a)、血管疾病、癌症和長壽

謝絹珠

脂蛋白(a)是一奇特的脂肪蛋白，其作用極具爭議色彩。脂蛋白(a)是由脂蛋白元(a)蛋白質以雙硫鍵方式鍵結於低密度脂蛋白的脂蛋白元 B 上，在許多族群的正常人，其血液中濃度分布曲線偏向較低方面 (每公升 0-200 毫克)，在心臟病及腦血管疾病中風病人脂蛋白(a)濃度偏高 (大於每公升 200 毫克)。過高的脂蛋白(a)似乎在人類會引起嚴重的疾病，但爲什麼在人類的進化史上保留此種脂肪蛋白？推測它應有對人類有益的特性，如覆蓋在血液中壞的膽固醇-低密度脂肪蛋白上、幫助受傷血管的修復及最近發現的抑制血管增生，進而抑制癌症細胞的生長。另外在百齡老人中，其血液中脂蛋白(a)濃度比正常人高，顯示可能與高齡長壽有關。脂蛋白(a)只存在於人類、猿猴及猬 (hedgehog) 上，人類血中沒有脂蛋白(a)並沒有疾病症狀，說明脂蛋白(a)並非絕對需要。這種謎樣的脂蛋白在人類進化的過程爲何被保留下來是個未解的謎題。(長庚醫誌 2011;34:555-64)

關鍵詞：脂肪蛋白元(a)，癌症，脂肪蛋白(a)，長壽，血管疾病

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