

LIPOPROTEIN (a)

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SUMMARY

Lipoprotein (a), Lp (a), is a spherical particle which floats at densities 1.05-1.1 g/ml. Lp(a) can be defined as a family of particles that contain apo B100 and highly glycosylated apo (a). Lp (a) is an independent risk factor for the development of coronary heart disease. High levels of Lp(a) are associated with premature myocardial infarction and cerebrovascular disease. The pathogenicity of Lp(a) may be due to its cholesteryl ester content contributing to the formation of foam cells. Apo (a) varies in size among individuals owing to different number of cystein-rich sequences that are homologous to kringle 4 of plasminogen. The size of the apo (a) gene correlates directly with the size of the apo (a) protein and inversely with the concentration of Lp(a) in plasma.

Key words: Lipoprotein (a), Lp(a), apo(a)

Lp(a) was first defined by Berg in 1963(1,2). Its significance in the development of coronary artery diseases and cerebrovascular thrombosis as an independent risk factor was realized in 1972 and very intense attention was given to Lp(a) after this date (3,4). Lp(a) is also responsible for the coronary artery bypass vein graft stenosis. In Lp(a), apoproteins apo B100 and apo(a) are in contact at one or more points by disulfide bridges (5). Reduction of the disulfide bonds results in separation of apo(a) from apo B100. Physicochemical and immunological properties of the remnant particle left after release of apo(a) resembles low density lipoprotein (LDL). Lp (a) may be regarded as a modified LDL particle, the modification giving the specific properties to the particle (6). Apo(a)-apo B100 complex that forms when hydrophilic apo(a) binds to apo B100 has both hydrophobic and hydrophilic properties (Fig.1). Although first assays were done on Lp (a) species that were rich in cholesterol esters in the core, later Bersot et al.

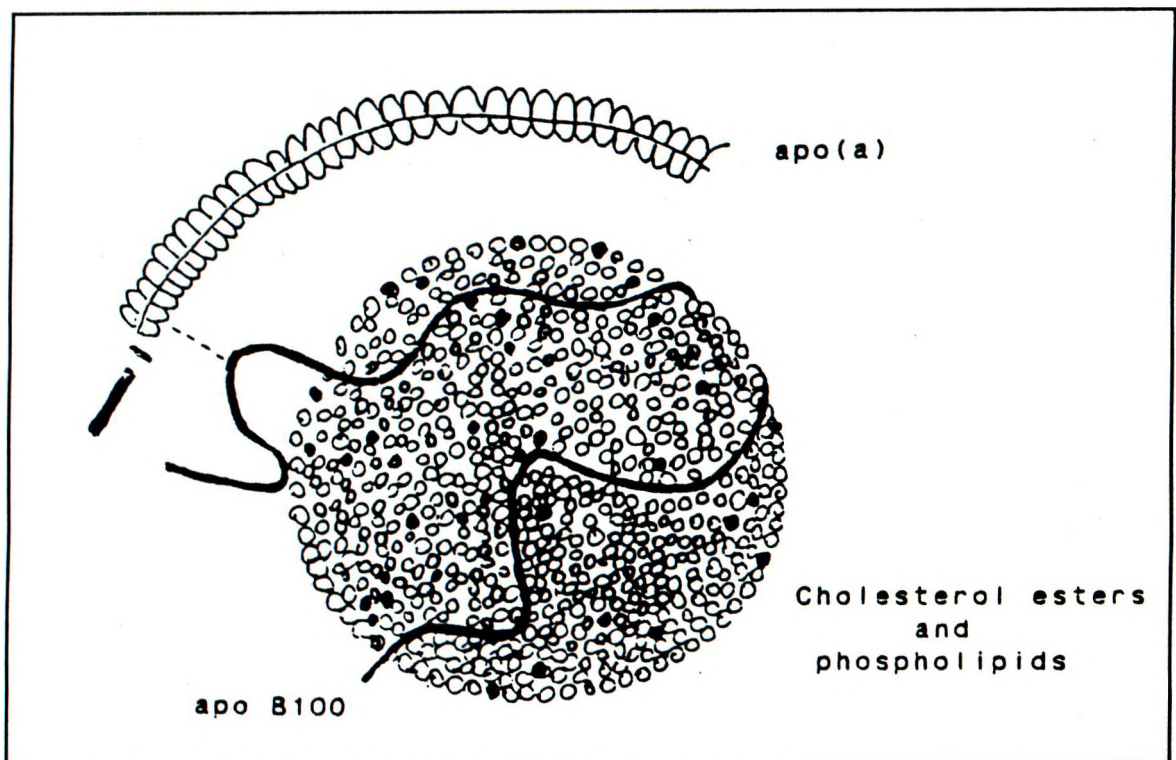


Fig. 1. Model of Lp(a). Lp(a) consists of a core of cholesteryl esters, a surface layer of phospholipids and free cholesterol and a molecule of apolipoprotein B100 linked to one molecule of apo (a).

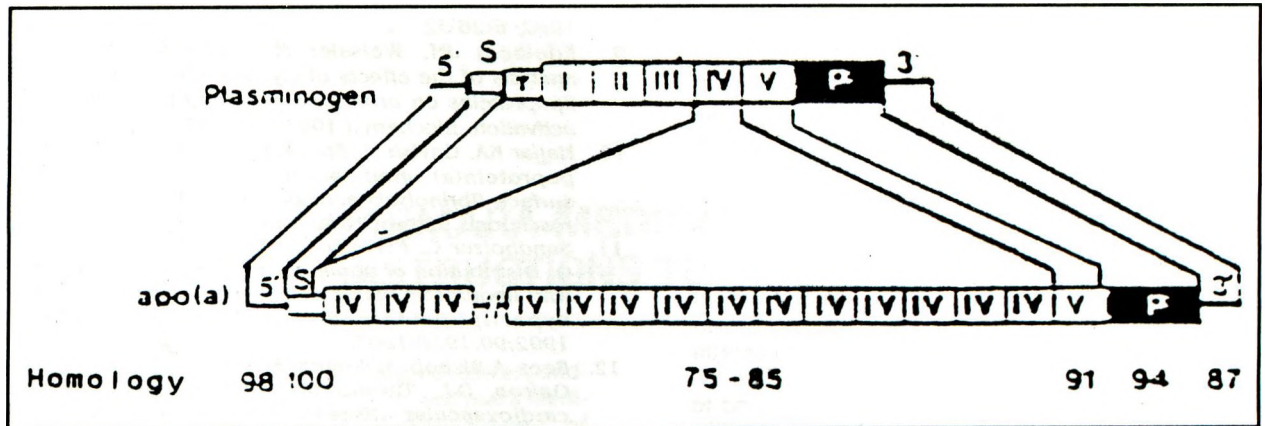


Fig. 2. Comparison of structural domains of plasminogen and apo (a) genes. S=signal peptide. T=tail or preactivation domain, I,II,III,IV,V=Kringle domains, P=protease domain

described the presence of apo(a) antigen in chylomicrons and chylomicron remnants postprandially. Intensive work is being done on the relationship between hypertriglyceridemia and Lp(a).

GENE STRUCTURE

The amino acid sequence of apo(a) was found to be highly homologous to plasminogen when Apo(a) cDNA was sequenced in 1987(7). Plasminogen has five structurally homologous regions which are called Kringles because of their similarity to a Danish breakfast roll. The Kringles of plasminogen have 50% homology. Apo(a) does not have the first three Kringles but has 15-37 of the Kringle IV, one Kringle V, 5' untranslated region, a signal peptide and a protease domain (Fig. 2). Of the 37 Kringle repeats, 24 are identical, the remaining copies differ by 3-71 nucleotides. Tissue plasminogen activator (t-PA), urokinase, coagulation factors VII, IX, X, XII and protein C also have Kringle like domains (8).

Kringle IV domains of apo(a) is thought to appear as a result of gene duplication and expansion about 40 million years ago. The reason for this evolution could be to compensate the low plasma cholesterol values of our ancestors because of different feeding habits. Lp(a) increases the risk factor for atherosclerosis in our present way of feeding.

Lp (a) AND THE FIBRINOLYTIC SYSTEM

Plasmin which is the cleavage product of plasminogen by t-PA, degrades fibrin (9). Apo(a) is not activated by tPA, urokinase, and streptokinase because of a point substitution at the place of action of these enzymes. Apo(a) has the ability to bind plasminogen receptors and macromolecules like fibrin, apo(a) competes with plasminogen in a dose dependent fashion in binding to plasminogen receptors on endothelial cell surfaces. It can disturb the critical balance between profibrinolytic and antifibrinolytic activities in high doses (10). This hypothesis is backed up with the fact that 20% of the

population whose Lp(a) levels are above 30 mg/dl has twice the risk of coronary atherosclerosis. Increase of LDL cholesterol together with Lp(a) increases this risk 4-5 times. Lp(a) was seen to be an equal risk factor in Japanese as well as the Caucasians (11). Studies with the Black population in Houston and Congo revealed that Lp (a) levels of this group were twice as much as that of Caucasians (12). High amounts of Lp(a) immunoreactive material was detected in the endothelial cells and intima of the arterial walls of the coronary bypass patients and that obtained by autopsy.

GENETICS OF Lp(a)

Apo(a) is inherited in a Codominant Mendelian fashion (13). No person has more than 2 types of apo(a) species. There is a direct relationship between the molecular weight and the Kringle number but there is an indirect relationship between the plasma Lp(a) level and the Kringle number (14).

Phenotyping is usually performed with immunoblotting and six phenotypes can be detected (15). A new sophisticated approach is the use of pulsed field gel electrophoresis of the restricted genomic DNA (16).

METABOLISM OF Lp(a)

Apo(a) which is synthesized in the liver complexes with apo B100 and is released into circulation. However the presence of Lp(a) which is rich in triglyceride makes us believe that there may be two different regulatory mechanisms.

Lp(a) passes through endothelial cells by transcytosis and is modified by the proteoglycans and glycosaminoglycans of the arterial wall matrix (17). The modified Lp(a) is then taken up by the scavenger receptor of the macrophages and gives rise to foam cell formation (18).

Lp(a) is metabolized independently from the other apo B containing lipoproteins, notably LDL. In vivo experiments with rabbits showed that ovaries take up significantly higher amounts of Lp(a) than LDL and there is a preferential uptake of Lp(a) by the kidney. It is suggested that the function of Lp(a) may be to supply cholesterol derived from the liver to peripheral tissues in a way which is independent of dietary influences (19).

Lp(a) levels do not change by age, environmental factors, and by diet. Niacin+Neomycin combination can lower the plasma levels by 30-40%. Lovastatin and Cholestyramine was not found to be effective. N-acetyl cystein which is a reducing agent is found to be promising (20).

It is known that Lp(a) levels increase after MI and surgical operations and fall back to previous levels in one month. Lp(a) acts like an acute phase reactant in this respect (21,22).

Screening the population for Lp(a) and lowering the LDL cholesterol of the ones with high Lp(a) levels may decrease the risk factors for atherosclerosis.

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