## Lipoprotein(a), athero-thrombosis and longevity. A historical paradox finally elucidated?

**Haematologica 2007;** 92:(4)e48

In a recent issue of this journal[1] it was concluded that lipoprotein(a) has an independent prothrombotic role through inhibition of fibrinolysis and by allowing an increased substrate for both platelet aggregation and thrombin, respectively. Accordingly, high levels of both lipoprotein(a) and fibrinogen, in addition to age and insulin, would be considered important risk factors for cardiovascular disease in the elderly. This conclusion apparently clashes with the results of several previous epidemiological surveys, concluding that elevated plasma lipoprotein(a) concentration is a rather frequent finding in centenarians.[2-6] This apparent paradox has engaged the minds of several scientists for many years, trying to find a reliable bridge between the cardiovascular potency of elevated concentrations of this elusive lipoprotein and human longevity.[7-8] Apolipoprotein(a), which characterizes lipoprotein(a), is constituted by an inactive protease domain, a single copy of the plasminogen kringle V and multiple repeats of domains homologous to the plasminogen kringle IV. The kringle domains, protein motifs arranged in a triple loop tertiary structure stabilized by three disulfide bridges, are highly conserved conformational regions hidden in the structure of a variety of members of the prothrombin gene family, including prothrombin, plasminogen, apolipoprotein(a), hepatocyte growth factor, urokinase, factor XII, tissue plasminogen activator.[8] Reliable studies on animal models have recently demonstrated that proteolytic break-down products of plasminogen, apolipoprotein[a] and other kringle-containing proteins endorse anti-angiogenic and antitumoral properties both *in vitro* and *in vivo*. In particular, apolipoprotein(a) fragments cleaved from the native protein by naturally occurring enzymes and specific tumour reductases, can maintain metastases in a dormant state and shrink primary tumors by blocking neovascularization and tumor growth *in vivo*, allowing prolonged survivals of animals bearing primary human malignancies.[9-11] This outstanding evidence would attribute to lipoprotein(a) an otherwise unexpected beneficial role beside its unfavourable cardiovascular potency and it would finally provide a reliable explanation for the historical paradox of elevated lipoprotein(a) levels associated with longevity.

*G. Lippi*, M. Franchini, G.C. Guidi*
*Sezione di Chimica e Microscopia Clinica,*
*Dipartimento di Scienze Morfologico-Biomediche,*
*Università degli Studi di Verona, Verona, Italy.**

*Correspondence. Prof. Giuseppe Lippi*
*Sezione di Chimica e Microscopia Clinica*
*Dipartimento di Scienze Morfologico-Biomediche*
*Ospedale Policlinico G.B. Rossi*
*Piazzale Scuro, 10, 37134 - Verona, Italy*
*Telephone: 0039-045-8124308, Fax: 0039-045-8201889*
*E-mail: giuseppe.lippi@univr.it; ulippi@tin.it*

### References

1. Marongiu F. High levels of lipoprotein (a) and fibrinogen: are they a dangerous association in the elderly? Haematologica 2006;91:1584.
2. Berg K, Ro OC. Lp(a) lipoprotein level and longevity. Ann Genet 1991;34:264-9
3. Thillet J, Doucet C, Chapman J, Herbeth B, Cohen D, Faure-Delanef L. Elevated lipoprotein(a) levels and small apo(a) isoforms are compatible with longevity: evidence from a large population of French centenarians. Atherosclerosis 1998;136:389-94
4. Pepe G, Di Perna V, Resta F, Lovecchio M, Chimienti G, Colacicco AM, Capurso A. In search of a biological pattern for human longevity: impact of apo A-IV genetic polymorphisms on lipoproteins and the hyper-Lp(a) in centenarians. Atherosclerosis 1998;137:407-17
5. Malaguarnera M, Giugno I, Ruello P, Rizzo M, Panebianco MP, Pistone G, Tomasello FB. Lipid profile variations in a group of healthy elderly and centenarians. Eur Rev Med Pharmacol Sci 1998;2:75-9
6. Arai Y, Hirose N, Nakazawa S, Yamamura K, Shimizu K, Takayama M, Ebihara Y, Osono Y, Homma S. Lipoprotein metabolism in Japanese centenarians: effects of apolipoprotein E polymorphism and nutritional status. J Am Geriatr Soc 2001;49:1434-41.
7. Lippi G, Guidi G. Lipoprotein(a): from ancestral benefit to modern pathogen? QJM 2000;9:75-84.
8. Berglund L, Ramakrishnan R. Lipoprotein(a): an elusive cardiovascular risk factor. Artherioscler Thromb Vasc Biol 2004;24:2219-26.
9. Yu HK, Kim JS, Lee HJ, Ahn JH, Lee SK, Hong SW, Yoon Y. Suppression of colorectal cancer liver metastasis and extension of survival by expression of apolipoprotein(a) kringles. Cancer Res 2004;64:7092-8.
10. Yu HK, Ahn JH, Lee HJ, Lee SK, Hong SW, Yoon Y, Kim JS. Expression of human apolipoprotein(a) kringles in colon cancer cells suppresses angiogenesis-dependent tumor growth and peritoneal dissemination. J Gene Med 2005;7:39-49.
11. Lee K, Yun ST, Kim YG, Yoon Y, Jo EC. Adeno-associated virus-mediated expression of apolipoprotein (a) kringles suppresses hepatocellular carcinoma growth in mice. Hepatology 2006;43:1063-73.