

The Mysteries of Lipoprotein(a) and Cardiovascular Disease Revisited*

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The discovery of lipoprotein(a) (Lp[a]) traces back to the 1960s, with fundamental insights into particle structure and heritability gained in the 1970s (1,2). Lipoprotein(a) is composed of a low-density lipoprotein (LDL) moiety and the covalently linked carbohydrate-rich apolipoprotein(a) (apo[a]), which is responsible for the unique properties of the particle. Lipoprotein(a) is a recent evolutionary arrival specific to humans and nonhuman primates, with the apo(a) component having originated from a duplication of the plasminogen gene. Like plasminogen, apo(a) is characterized by loop structures called kringles. It contains an inactive protease domain, 1 kringle V and 10 different types of kringle IV motifs, with the kringle IV type 2 (KIV₂) occurring in multiple copies (3 to 50) regulated by a copy-number variation in the *apo(a)* gene. The heterogeneity in the number of KIV₂ copies accounts for approximately one-half of the substantial (up to 1,000-fold) interindividual variability of Lp(a) plasma levels. Recent large-scale surveys unraveled a complex genetic architecture of Lp(a) beyond the classic copy-number variation (3,4). Multiple (low-prevalence) single-nucleotide polymorphisms in the Lp(a) locus on chromosome 6q were reported to partly explain the wide range of Lp(a) levels in carriers of the same *apo(a)* isoform and discrepancy in Lp(a) levels between people of African descent and whites.

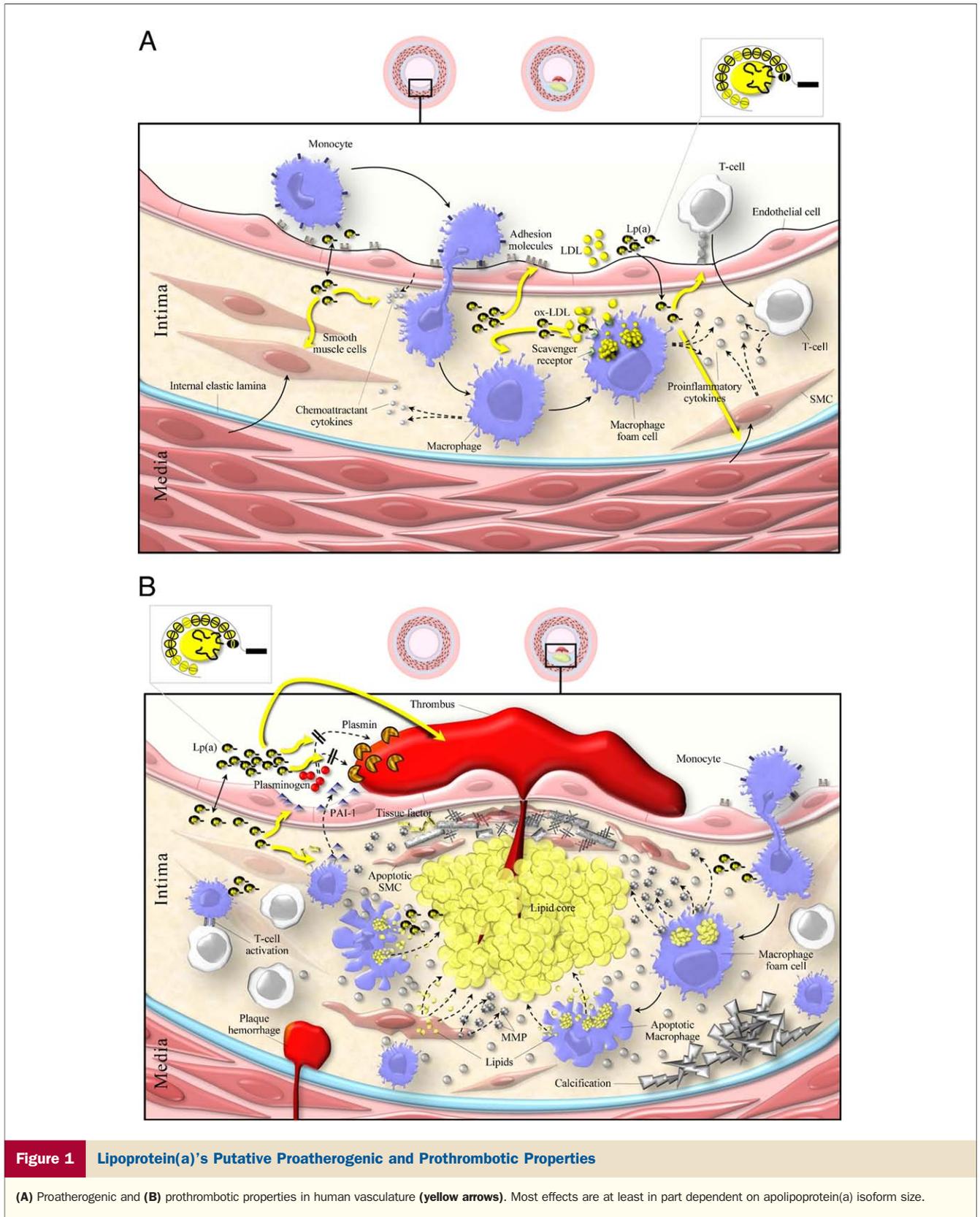
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Lipoprotein(a) does not bind to the LDL receptor, and accordingly, Lp(a) levels in circulation are not determined by the efficacy of particle clearance but primarily by its synthesis. The well-founded inverse relationship between Lp(a) concentration and apo(a) size arises from the lower secretion rates in hepatocytes of large *apo(a)* isoforms. As a consequence, the smaller apo(a) phenotype usually dominates in individuals with 2 distinct *apo(a)* alleles.

Since its discovery, Lp(a) has been recognized to predict the progression of atherosclerosis and manifestation of its main clinical sequelae, myocardial infarction (5,6). A true risk factor status is strongly corroborated by the: 1) pathohistologic observation that Lp(a) particles accumulate in human atherosclerotic lesions, especially culprit plaques prone to rupture, but not in normal vasculature; 2) emergence of highly significant associations between genetically elevated levels of Lp(a) and cardiovascular disease, found by employing Mendelian randomization approaches (3); and 3) amplification of plaque area in atherosclerosis-susceptible transgenic mouse and rabbit models expressing apo(a) (6,7). Lipoprotein(a) has been invoked to exert both proatherogenic and prothrombotic effects in multiple stages of the atherosclerosis process, some of which are apo(a)-dependent and others primarily related to the LDL component. In brief, Lp(a) was shown to promote smooth muscle cell migration and proliferation by interference with transforming growth factor- β activation, induce monocyte chemotactic activity, stimulate endothelial adhesion molecule expression, and give rise to foam cell formation and lipid-induced atherogenesis analogous to genuine LDL particles but probably more potent owing to a prolonged residence time in the vessel wall afforded by its affinity to arterial proteoglycans and interaction with fibrin (Fig. 1A). Two injurious capacities deserve privileged attention. First, an intriguing feature of apo(a) is the approximately 80% structure homology with plasminogen, a key component of the endogenous fibrinolytic system. Because the protease domain of apo(a) lacks catalytic function, Lp(a) acts as a competitive inhibitor for plasminogen activation (Fig. 1B), with this capacity being more pronounced for low-molecular-weight (LMW) apo(a) isoforms (8). Beyond impairment of clot lysis, Lp(a) was reported to promote thrombus formation by potentiating platelet aggregation and stimulating plasminogen activator inhibitor expression in and release from endothelial cells and monocytes (Fig. 1B). Epidemiologic evidence for a prothrombotic action of Lp(a) in vivo is sparse. Analyses in the Bruneck cohort revealed a highly significant association between LMW, but not high-molecular-weight, apo(a) phenotypes and advanced atherogenesis primarily featured by plaque thrombosis (9). In a recent study (10), LMW

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apo(a) phenotypes were found to be related to stroke of atherothrombotic origin, but not to other stroke subtypes. Second, Lp(a) was proposed to act as the main scavenger for

oxidized phospholipids (OxPLs) in human circulation and to mediate clearance of these proinflammatory and proatherogenic adducts via cleavage through lipoprotein-

associated phospholipase A₂ (Lp-PLA₂) (7). The potential benefit of OxPL binding, however, may turn into harm if high levels of Lp(a) with its OxPL load recirculate into the vasculature. Both in vitro experiments and in vivo studies in humans and transgenic mice expressing Lp(a) demonstrated that the vast majority of OxPLs detected by the monoclonal antibody E06 travels on Lp(a) (7,11). Of note, the correlation between OxPL and Lp(a) levels is very strong in individuals with small apo(a) isoforms ($r = \sim 0.95$), but less so in individuals with larger isoforms ($r = \sim 0.5$ to 0.7). Likewise, Lp-PLA₂ activity is several-fold higher on Lp(a) of individuals with elevated Lp(a) levels and LMW apo(a) isoforms than in equimolar amounts of LDL (7). Transgenic mice with mutant apo(a) unable to bind OxPLs have been developed and will clarify the exact contribution of OxPLs to the atherogenicity of Lp(a). Overall, compelling evidence from atherosclerosis research suggests that Lp(a) is a potent vascular risk factor and that both Lp(a) concentration and apo(a) phenotype do matter in this scenario.

In this issue of the *Journal*, a stimulating meta-analysis by the team of John Danesh and Santica Marcovina (12) adds the first large-scale epidemiologic support to a specific role of apo(a) in cardiovascular disease. That team completed a challenging and skillful job in combining aggregated data from 40 individual studies with considerable heterogeneity in laboratory methods and analytic approaches and demonstrated that subjects with LMW and high-molecular-weight apo(a) phenotypes—separated by a cut-off of approximately 22 KIV₂ repeats and encompassing about 40% and 60%, respectively, of the white population—differ in their risk for myocardial infarction and stroke by a factor of approximately 2. The strength of association apparently surpassed that obtained for Lp(a) concentration and vascular disease in a recent meta-analysis including 126,634 individuals (13). Major novelties of the current study are its considerable size, its focus on both myocardial infarction and stroke, documentation of consistent associations for a wide range of circumstances, and various analytic methods of apo(a) phenotype and genotype assessment (12). Important issues that remain to be addressed are the identification of precise scales of association and actual cut-off values (if any), determination of the extent of independency of apo(a) phenotype findings from Lp(a) level, and assessment of effect modification by other novel biomarkers. There is preliminary evidence that Lp(a) affects cardiovascular disease risk, conditional on the level of (small-dense) LDL, OxPL concentrations, and Lp-PLA₂ activity (5–7,14).

Several studies in the general community and in patients with advanced kidney disease alike have suggested that assessing apo(a) isoforms is of predictive utility above and beyond the information provided by Lp(a) levels. However, formal proof that apo(a) assessment allows for a relevant reclassification of individual subjects between cardiovascular risk strata and a significant gain in model discrimination and calibration remains to be furnished.

Is it time to transfer all of these advances into clinical practice? Not yet, but after almost 4 decades of uncertainties in Lp(a) research, the puzzling pieces of knowledge are being assembled to a promising whole. We are on the verge of understanding the physiologic role and pathologic properties of Lp(a) particles and await the development of specific Lp(a)-lowering therapies. Urgent steps to take are to: 1) characterize potential joint effects of Lp(a)/apo(a), OxPL, (small-dense) LDL, and Lp-PLA₂ on atherosclerosis; 2) clarify which analytic approach of apo(a) assessment (6,12) best fits the clinical demands; and 3) rigorously test extended risk scores considering Lp(a) level, apo(a) isoforms, or both, on top of standard risk factors in various ethnic groups. Concerted efforts are required to bring more than 40 years of mysteries and surprises in Lp(a) research to a successful end.

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