Lipoprotein(a)

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Lipoprotein(a): The Renaissance of an Enigmatic Lipoprotein

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Human plasma contains lipoprotein(a) [Lp(a)], a macromolecular complex that consists of a low density lipoprotein (LDL) particle to which a glycoprotein, known as apolipoprotein (a) [apo(a)], is linked via a disulfide bond to apolipoprotein B100 (apoB100), the principal protein that is carried on LDL particles (1, 2). Ever since the discovery of this lipoprotein in 1963 by Kåre Berg (3), Lp(a) has intrigued clinicians and researchers because of its complex genetics and its enigmatic regulation.

Similar to plasminogen, apo(a) contains loop-like structures, called kringles (4). Besides kringle IV-1 (KIV-1), human apo(a) contains KIV-2 to KIV-10, KV and a probably inactive protease domain (4). Apo(a) is highly heterogeneous in size. Smaller apo(a) isoforms are associated with higher plasma levels of Lp(a). Variable numbers of tandemly repeated exon sequences in the *LPA* locus (chromosome 6q2.6-q2.7) encoding KIV-2 of apo(a), a form of copy number variation (CNV), give rise to considerable size polymorphism of the apo(a) protein (4). The circulating level of Lp(a) is strongly and inversely determined by the KIV-2 copy number in apo(a), explaining to a considerable extent the marked variation in plasma Lp(a) levels between individuals (1, 4). Lp(a) also varies between individuals of different ethnicities with people of black ethnicity generally having higher levels than people of white and Asian ethnicity (1, 4). In humans, Lp(a) is predominantly, if not exclusively produced, by the liver (4). The process of Lp(a) assembly and release in the circulation is not precisely known, but involves covalent binding of apo(a) to apoB100 via the formation of a disulfide bridge between these protein moieties (4). However, it is unclear whether Lp(a) assembly is primarily an intracellular event or takes places at the surface of hepatocytes or even in the extracellular space. Nonetheless, while very low density lipoproteins (VLDLs) are considered precursors of LDLs, there is virtually no correlation of VLDL-apoB100 nor of LDL-apoB100 production with apo(a) production (5), suggesting that apoB100 and apo(a) influx in the extracellular compartment are to a considerable extent unrelated processes. Furthermore, the molecular mechanisms responsible for Lp(a) catabolism still remain elusive, although the catabolism apo(a) and apoB100 in Lp(a) particles are tightly coupled. Several receptor systems that include lipoprotein receptors, toll-like and scavenger receptors, lectins, and plasminogen receptors have been proposed to be implicated in Lp(a) catabolism (6). Of interest, the toll-like receptor-2 was the only receptor that was associated with Lp(a) in a genome wide association study (6). The importance of the LDL receptor for Lp(a) catabolism has not yet been fully elucidated (1, 4). Plasma Lp(a) is clearly elevated in some patients with heterozygous familial hypercholesterolemia in the context of certain dysfunctional variants in the *LDLR* gene encoding the LDL receptor, in the *APOB* gene that alter apoB-100 receptor binding, and in gain-of-function

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Abbreviations: apo(a), apolipoprotein(a); apoB100, apolipoprotein B100; CNV, copy number variation; CVD, cardiovascular disease; GH, growth hormone; HDL, high density lipoprotein; KIV, kringle IV; LDL, low density lipoprotein; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL, very low density lipoprotein.

mutations in *PCSK9* encoding proprotein convertase subtilisin/kexin type 9 (7, 8). By contrast, statins, which act by increasing LDL receptor availability on the surface of hepatocytes, do not lower but—on the contrary—may even increase plasma Lp(a) (9).

A large body of evidence has now been accumulated to indicate that high plasma Lp(a) is associated with increased risk of newly developed and recurrent atherosclerotic cardiovascular disease (CVD) events [reviewed in (1, 2)]. Of further note, Mendelian randomization studies have evaluated several forms of genomic variation in *LPA*, including single nucleotide polymorphisms (SNPs) and CNV in the KIV-2 coding sequence, and have shown that both types of variation on *LPA* are causally related to atherosclerotic CVD in individuals of various ethnicities tested (10–12). In fact, variation in *LPA* is considered to represent the single strongest lipid genetic risk factor for CVD (1).

Apo(a) immunoreactivity is detectable in atherosclerotic plaques. Several pro-atherogenic mechanisms of Lp(a) have been proposed (1, 4). However, the extent to which Lp(a) may interfere with clotting and fibrinolytic actions *in vivo* is not well known. Importantly, Lp(a) is the preferred lipoprotein carrier of oxidized phospholipids, suggesting a mechanism whereby Lp(a) may promote pro-inflammatory pathways in the arterial wall (13). Interestingly, oxidized phospholipids on apoB100 associate with *LPA* variants, underscoring the idea that oxidized phospholipids form part of the process whereby Lp(a) exerts its pro-atherogenic properties (11).

Besides the paramount contribution of genetic variation in *LPA*, Lp(a) is also subject to hormonal regulation (1). Lp(a) levels are increased in overt hypothyroidism (1) and are rapidly lowered after triiodothyronine supplementation in individuals with profound hypothyroidism (14). An Lp(a)-decreasing effect has also been found in response to thyromimetics (15). There are no major sex differences in Lp(a), but its level is higher in postmenopausal *vs* premenopausal women. Estrogens and androgens may both decrease Lp(a) (1). Levels of Lp(a) are increased in the context of acromegaly (1, 16). Likewise, Lp(a) may increase in response to growth hormone growth hormone (GH) administration in GH-deficient adults, an effect which is opposite of the decrease in LDL cholesterol and non-high density lipoprotein (non-HDL) cholesterol (1, 17). Intriguingly, lower Lp(a) levels may confer increased risk of developing type 2 diabetes (18). Plasma Lp(a) is also elevated in chronic kidney disease, as well as in the nephrotic syndrome (1)

In order to improve the rationale for Lp(a) targeted therapies it is important to discern mechanisms responsible for its regulation. One valuable approach is to apply stable isotope kinetic modelling to interrogate Lp(a) metabolism (19). Such techniques are methodologically difficult and are critically dependent on the isolation of Lp(a), required to be devoid of other lipoproteins that contain apoB (19). Moreover among other uncertainties, the mathematics of the kinetic model applied are dependent on the assumption as to whether apo(a) is recycled in the circulation (19). In a recent issue of *JCEM*, Ma *et al* report on apo(a) kinetics in patients at high CVD risk who are receiving statin therapy (20). Using labor intensive stable isotope methodology and isolation of apo(a) by immunoprecipitation followed by sodium dodecyl sulfate gel electrophoresis and Western blotting, they showed that the production rate of apo(a) is increased in subjects with elevated plasma Lp(a) compared with individuals who have normal levels of Lp(a). Notably, no difference in apo(a) fractional catabolic rate between the high and low Lp(a) groups was found (20). In another recent study among statin-treated subjects, the same research group reported that the apo(a) fractional catabolic rate was similar compared with that of apoB, irrespective of whether plasma Lp(a) was elevated (21). In comparison, an early report by Rader *et al* in which Lp(a) was labelled with radioactive iodine revealed a strong correlation of plasma Lp(a) with its production rate but not with its fractional catabolic rate among healthy young adults (22).

Thus for many reasons, Lp(a) has regained interest as CVD risk biomarker. Lp(a) measurement may be useful to improve CVD risk classification in selected patients, including those who have suffered a recurrent event (2). Notwithstanding the modest decrease of Lp(a) in response to PCSK9 inhibitor treatment (23), there remains an unmet need to reduce Lp(a) in high-risk patients in whom it is elevated. Evidence is accumulating in support of the possibility that increased plasma Lp(a) concentrations, which coincide with smaller-sized apo(a) isoforms, are primarily due to increased hepatic production. These findings provide a rationale to develop Lp(a)-targeted therapies directed toward inhibition of its synthesis. Treatment based on antisense technology is currently being tested, but its efficacy and safety still have to be proven in CVD outcome studies. It is hoped that such treatment will reach the clinic in the near future.

Additional Information

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