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# Recent advances in demystifying the metabolism of lipoprotein(a)

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## ABSTRACT

Lipoprotein (a) (Lp(a)) is a strange lipoprotein species causatively independently and significantly associated with cardiovascular diseases and calcified aortic valve stenosis. Elevated plasma Lp(a) levels increase the rate of cardiovascular events at any achieved low-density lipoprotein (LDL) level. The major structural difference between Lp(a) and LDL is that Lp(a) has a second large protein, apolipoprotein (a) (apo(a)), bound to the apolipoprotein B100 moiety of an LDL sized particle by a single disulfide bond.

Over the past decades, several investigators have tried to elucidate the molecular, cellular and metabolic pathways governing the production of Lp(a), the contribution of Lp(a) to lipid transport in the plasma, and the catabolic fate of Lp(a). The metabolism of this enigmatic lipoprotein nevertheless still remains poorly understood.

The objectives of the present manuscript are to comprehensively review the knowns and unknowns of the complexities of Lp(a) metabolism with a focus on apo(a) biosynthesis in hepatocytes, Lp(a) assembly, and Lp(a) plasma clearance and catabolism. We also discuss the controversy surrounding the exact role of the LDL receptor in mediating Lp(a) cellular uptake by reviewing seminal *in vitro* and *in vivo* data, the metabolism of Lp(a) in familial hypercholesterolemia, as well as the divergent effects of statins and proprotein convertase subtilisin kexin type 9 inhibitors in modulating Lp(a) plasma concentrations. We also provide new insights into the physiology and pathophysiology of Lp(a) metabolism from human kinetic studies in the context of contemporary molecular and cell biological investigations.

### Key points box 1: The metabolism of Lp(a)

- Lp(a) consists of an LDL sized particle covalently linked to the unique glycoprotein, apo(a).
- Lp(a) assembly in the liver is a two-steps process: apo(a) and apoB100 associate non-covalently intracellularly and a disulfide bond is formed between apo(a) and apoB100 at the cell surface.
- Unlike LDL, Lp(a) is not the catalytic product of triglyceride rich lipoproteins metabolism.
- The liver is the major site of Lp(a) uptake. Multiple pathways have been proposed, in particular the LDL receptor, but there is no consensus regarding its exact contribution to Lp(a) plasma clearance.
- Major gaps in knowledge persist and the identification of the mechanistic processes governing Lp(a) biology remain to be elucidated.

## **1-Introduction**

Lipoprotein (a) (Lp(a)) is a polymorphic particle that is causatively associated with cardiovascular and calcified aortic valve disease [1,2]. Pathophysiological, epidemiological and genetic studies demonstrate that elevated plasma Lp(a) levels dose-dependently increase the risk of cardiovascular events, as discussed in other reviews of this review series [3,4].

Lp(a) consists of an LDL sized particle covalently linked to the unique glycoprotein, apo(a). A key feature of Lp(a) is the potent genetic determination of its plasma concentrations, which range over 1000-fold distribution in the population. The *LPA* gene encodes apo(a) on chromosome 6 and accounts for more than 90% of the variation in plasma concentrations [5]. *LPA* alleles contain a variable number of exons pairs encoding the plasminogen-like kringle IV (KIV) domains [6,7]. This results in different apo(a) isoforms, ranging from 300 to 800kDa, corresponding to the presence of one to 40 KIV type 2 (KIV<sub>2</sub>) domains [8–12].

## **2- Metabolism of lipoprotein(a)**

None of the common animal models naturally presents the Lp(a) trait, which limits the accurate investigation of the biology of Lp(a) *in vivo*. Very different and sometimes inappropriate, or non-physiological, cellular and animal model systems have been used to explore the molecular and cellular pathways governing the synthesis, assembly, secretion, and catabolism of Lp(a); this has resulted in many discrepant findings. Due to this limitation, results from studies using these model systems remain questionable, in particular when *in vitro*, *in vivo*, and human kinetic studies yield opposite conclusions. Key points and major limitations on the current knowledge of Lp(a) metabolism are summarized in [Box 1].

### **2.1- Synthesis, assembly and secretion**

Like apoB100, apo(a) is exclusively synthesized in hepatocytes [13] and undergoes post-translational modifications in the ER, including the formation of three disulfide bonds within each kringle motifs as well as N-glycosylations. The residence time of apo(a) isoforms in the ER is proportional to their number of KIV<sub>2</sub> domains [14–16]. As a result, large apo(a) isoforms are more susceptible to proteosomal degradation [15,17], which may explain why circulating plasma Lp(a) concentrations are on average higher in carriers of short apo(a) isoforms [18,19]. Subsequently, apo(a) is translocated to the Golgi apparatus, where it is further N-glycosylated and O-glycosylated. Even if carbohydrates can comprise up to 28% of the molecular weight of apo(a), impairment of glycosylation does not appear to alter its ability to associate with

apoB100 [20]. The availability of apoB100 could be rate limiting for Lp(a) synthesis, as suggested by studies conducted in patients with abetalipoproteinemia [21], or in FH patients treated with mipomersen or lomitapide that target the expression of apoB100 and microsomal triglyceride transfer protein, respectively [22].

Unlike LDL, Lp(a) is not the direct product of very low-density lipoproteins (VLDL) sized particles metabolism [23]. Kinetic studies suggest that any apo(a) coupled with VLDL is unlikely to be a precursor of Lp(a) [5,24]. On the other hand, several earlier studies indicated that the process of Lp(a) assembly likely occurs extracellularly or at the cell surface following hepatic secretion of apo(a) [14,16,19,25–29]. This has, however, been challenged by studies showing that apo(a)-apoB100 complexes can be detected intracellularly [30–32].

Experimental work shows that Lp(a) assembly is a two-steps process: first, apo(a) and apoB associate non-covalently through the interactions between weak lysine binding sites located in apo(a) KIV<sub>7</sub> and KIV<sub>8</sub> domains and Lysine residues located on apoB100 [32–40]; second, a disulfide bond is formed between the only “free” Cysteine of apo(a) located in its KIV<sub>9</sub> domain [Cys<sub>4057</sub>] and a Cysteine located in the C-terminal domain of apoB100 [Cys<sub>4326</sub>] [7,26,41–47] (**FIGURE 1**). Cell culture and *in vivo* kinetic studies collectively indicate that the non-covalent association between apoB100 and apo(a) takes place within hepatocytes. A recent report elegantly demonstrates the existence of non-covalent apo(a)-apoB100 complexes within the secretory pathway in HepG2 cells [32]. The covalent attachment, which is enzyme-catalyzed, occurs extracellularly [12,29,48–50]. The enzyme governing this process remains to be characterized.

Several *in vivo* models have been proposed to address the unanswered questions regarding the assembly and secretion of Lp(a) (**FIGURE 2**) [51]. In the first model (Model 1), Lp(a) particles are assembled within or at the surface of hepatocytes, so that newly synthesized Lp(a)-apoB100 and Lp(a)-apo(a) have identical isotopic enrichment curves in plasma and similar fractional catabolic rates (FCRs), or fractional synthetic rates. In the second model (Model 2), apoB100 and apo(a) combine to form Lp(a) within or at the surface of hepatocytes, but Lp(a)-apo(a) is degraded and some apoB100 is recycled to the Lp(a) assembly site after a circulating Lp(a) is taken up by the liver. In this model, Lp(a)-apoB100 will have a lower isotopic enrichment curve and FCR than Lp(a)-apo(a). By contrast to Model 2, the third model (Model 3) proposes that apoB100 and apo(a) combine to form Lp(a) within or at the surface of hepatocytes, as in Models 1 and 2; after uptake by the liver, the Lp(a)-apoB100 is degraded whereas a proportion of Lp(a)-apo(a) is recycled to the Lp(a) assembly site, resulting in Lp(a)-apoB100 having a higher

isotopic enrichment curve and FCR than Lp(a)-apo(a). Using stable isotope tracers and compartmental modelling, we demonstrated that in individuals with a wide range of plasma Lp(a) concentrations, the isotopic tracer curves for Lp(a)-apoB100 and Lp(a)-apo(a) were essentially identical, with similar contour and area-under-curve [52]. This notion was confirmed in another kinetic study of statin-treated patients with elevated and normal Lp(a) concentrations [53]. Hence, these kinetic data generally support Model 1 positing that newly synthesized Lp(a)-apoB100 and Lp(a)-apo(a) are secreted as a holoparticle with tightly coupled apo(a) and apoB100 residence times in the circulation. However, only the kinetics of the major apo(a) isoform in the post-absorptive state were investigated in these studies. Whether the same finding applies in the postprandial state or to the metabolism of minor apo(a) isoform remains to be investigated.

## **2.2 Clearance and catabolism**

The mechanisms of Lp(a) clearance from the circulation and the catalytic pathways involved also remain uncertain [11,12,54]. Nevertheless, it is well established that the liver is the major site of Lp(a) clearance followed to a much lesser extent by the kidney and the arterial wall [55–57]. Aortic-renal vein gradient studies suggest that the kidney can extract Lp(a) from the circulation [58], and fragments of apo(a) Kringle domains are excreted in the urine [59,60]. A role for the kidney in the metabolism of Lp(a) is also supported by the inverse correlation between plasma Lp(a) and glomerular filtration rate (GFR), with a significant increase in Lp(a) in patients with more advanced chronic kidney disease (CKD) [61,62].

Multiple alternative pathways for Lp(a) clearance have been proposed. For example, a large genome wide association study (GWAS) has indicated that TLR2 is the only receptor associated with circulating Lp(a) concentrations. This receptor is a signaling receptor that triggers apoptosis in Lp(a) stimulated macrophages, and is not formally a clearance receptor [63,64]. In contrast, the scavenger receptor BI (SR-BI) has been shown to promote the selective uptake of Lp(a) cholesterol esters in cells and in SR-BI transgenic and knockout mice [65]. In that respect, SR-BI genetic variants are associated with elevated Lp(a) concentrations in two cohorts [66]. Carbohydrate-binding proteins (lectins), such as the asialoglycoprotein receptor (ASGPR), have also been shown to act as Lp(a) receptors in mice [56], but not all findings agree [55,67]. Given the strong homology between apo(a) and plasminogen, the role of plasminogen receptors in mediating Lp(a) clearance has been investigated [68]. One of such receptors, the plasminogen receptor presenting a C terminal lysine (PLGR<sub>KT</sub>), was shown to mediate the cellular uptake of Lp(a) by human hepatoma cells and primary human fibroblasts. This study also showed that

the LDL component of Lp(a) undergoes lysosomal degradation whereas apo(a) traffics through recycling endosomes and is re-secreted into the medium [67]. However, the concentration of free apo(a) in human plasma is low [less than 5% of total circulating apo(a)] and mostly consists in apo(a) degradation products [69], which suggests minimal recycling of apo(a) in the circulation.

Several members of the LDLR family of receptors have also been proposed to mediate whole Lp(a) particle cellular uptake. Thus, the VLDL receptor binds apo(a) and allows the internalization and subsequent degradation of Lp(a) in macrophages [70]. The LDLR related protein 1 (LRP1) and megalin/gp330 (known as LRP2) also play a role in Lp(a) binding, cellular uptake and degradation *in vitro* [71–73]. LRP8 (formerly known as the apoB,E receptor) is also able to bind Lp(a) at the plasma membrane, but it remains to be shown whether this promotes cellular uptake and degradation of Lp(a) particles [74,75]. The cellular uptake of Lp(a) was however recently shown to be unaffected in HepG2 hepatoma cells overexpressing either the VLDLR, LRP1 or LRP8 [76] (**FIGURE 3**).

### **2.3- Role of the LDL receptors in lipoprotein(a) clearance?**

Given the important structural similarities between LDL and Lp(a), the LDL receptor has received most attention as a candidate receptor for Lp(a) over the past decades. It is well established that statins, that enhance LDLR expression and thereby markedly reduce LDL, have a neutral, or an elevating, effect on plasma Lp(a) concentrations [77,78]. Unexpectedly, PCSK9 inhibitors, which also increase the cell surface expression of the LDLR, via an inhibition of LDLR intracellular degradation, not only lower LDL-C (by 50-60%), but also reduce plasma Lp(a) concentrations (by 20-30%) [79]. This observation has renewed research into the roles of PCSK9 and of the LDLR in mediating the clearance of Lp(a) from the circulation [11].

#### **2.3.1 *In vitro* studies**

Initial reports showed that Lp(a) can bind to the LDLR with a lower affinity than LDL [72,80–83]. Lp(a) was also proposed to associate with LDL and undergo LDLR mediated clearance via a “hitch-hiking” mechanism [84,85]. In HepG2 and primary human fibroblasts, PCSK9 was shown to reduce the binding and the cellular uptake of Lp(a) via the LDLR [86,87]. These results were confirmed in HuH7 hepatoma cells and primary murine hepatocytes [76]. In contrast, other studies found no significant role for the LDLR in mediating the cellular uptake of Lp(a) in primary human hepatocytes, fibroblasts and HepG2 cells [67,88,89]. Moreover, no significant difference was found in the cellular uptake of Lp(a) in primary lymphocytes derived

from normolipaemic individuals compared with patients with homozygous familial hypercholesterolemia (FH) and complete absence of LDLR function [90]. It is noteworthy that LDLR expression in human primary lymphocytes is positively and significantly correlated with plasma LDL-C concentration, but not with plasma Lp(a) concentrations [91].

### ***2.3.2 In vivo studies***

Studies in mice, rabbits and non-human primates have also yielded opposite conclusions regarding the role of the LDLR, as well as on the effects of PCSK9 inhibitors on Lp(a) catabolism. Thus, compared with wild-type animals, mice overexpressing the LDLR display accelerated Lp(a) plasma clearance [92], but LDLR knockout mice have similar Lp(a) clearance to wild-type mice [55]. Furthermore, the catabolism of Lp(a) in rabbits is slower than that of LDL, suggesting that Lp(a) uptake is not fully dependent on the LDLR and may be mediated by other mechanisms [93]. In addition, while the PCSK9 inhibitor, alirocumab, did not influence the catabolic rate of Lp(a), it enhanced the production of Lp(a) in the non-human primate model [94]. Also, alirocumab had no effect on the hepatic capture of Lp(a) in liver-humanized mice [90].

### ***2.3.3 Familial hypercholesterolemia as a model for understanding the metabolism of Lp(a)***

Early studies of FH and non-FH siblings with identical apo(a) isoforms demonstrated that Lp(a) was approximately two-fold higher in FH patients than controls [95]. FH homozygotes with two non-functional LDLR alleles also display 2-fold higher Lp(a) levels than their heterozygote relatives [96]. Likewise, familial ligand-defective apoB100 FH patients (FDB) have higher Lp(a) than non-FDB family members [97], and PCSK9 gain-of-function mutations carriers also similarly display higher Lp(a) than non-FH controls [98].

However, the notion that Lp(a) is higher in FH patients has recently been challenged by two independent cohort studies. In 46,200 individuals from the Copenhagen General Population Study, mean Lp(a) concentrations were 23mg/dL in individuals unlikely to have FH, 32mg/dL in possible FH, and 35mg/dL in probable or definite FH, based on the Dutch Lipid Clinics Network diagnostic criteria [99]. However, after adjusting LDL-C levels for Lp(a) cholesterol to more accurately assess the FH status, those values were similar at 24, 22 and 21 mg/dL, respectively. This result needs to be considered cautiously, however, since the accuracy of the correction factor used in this study to adjust LDL-C for Lp(a)-cholesterol remains uncertain [100,101]. Similar observations were made in the British Columbia FH cohort [102]. In that cohort, elevated Lp(a) levels in FH were linked to a 2-fold higher prevalence of a specific single nucleotide polymorphism (rs10455872) on the *LPA* gene associated, with an average 64 mg/dL



increase in circulating Lp(a) levels [102] compared with the reference population, suggesting ascertainment bias in the association between FH and elevated Lp(a). The authors further investigated this possibility using whole exome sequencing by identifying 221 “true” FH patients (i.e. with pathogenic mutations on the *LDLR*, *APOB*, or *PCSK9* genes) out of 37,486 individuals in the UK biobank, without prior knowledge of their clinical history. As anticipated, these 221 individuals had significantly higher plasma levels of LDL-cholesterol than the 37,265 non-FH individuals, but both groups had similar plasma concentrations of Lp(a) [102]. These new data cast doubt on the consensus that Lp(a) is elevated in FH, questioning the validity of the much smaller earlier studies.

Very few studies have specifically investigated the clearance of Lp(a) in patients with FH. Using exogenous radiolabeled tracers, Rader *et al.* found that the clearance of Lp(a) did not differ significantly among homozygous FH patients, heterozygous FH parents and non-FH control subjects [103]. In a recent stable isotope tracer study, Croyal *et al.* reported that the FCRs of Lp(a)-apo(a) were similar in patients with PCSK9 gain-of-function mutations and control subjects [104]. Hence, defects in LDLR function do not appear to result in delayed clearance of Lp(a). In a study of healthy normolipidemic men, there was no significant association between the FCRs of apo(a) and LDL-apoB100 [105]. These kinetic findings suggest that the LDLR may not play a major role in Lp(a) clearance. However, the role of the LDL receptor in Lp(a) clearance in patients with concomitantly high LDL-cholesterol and high Lp(a) who are treated with a combination of statins and PCSK9 inhibitors has not been specifically investigated.

In aggregate, the aforementioned studies do not provide a clear consensus regarding the exact contribution of the LDLR to the clearance of Lp(a) from the circulation. To summarize, a role of the LDLR in mediating Lp(a) clearance is supported by the following evidence: (i) FH patients with LDLR defects usually display higher Lp(a) levels than non-affected relatives; (ii) Lp(a) binds to the LDLR *in vitro*; (iii) there is a large structural homology between LDL and Lp(a) particles; (iv) overexpression of LDLR in mice accelerates Lp(a) clearance; (v) PCSK9 inhibitors reduce Lp(a) and most correlations observed between changes in LDL and changes in Lp(a) following PCSK9 inhibitors treatments are positive and significant. By comparison, a non-LDLR mediated pathway is supported by the following evidence: (i) up-regulating the LDLR even with the most potent statins does not lower Lp(a) concentration, (ii) there is no correlation between the levels of LDLR expression assessed *ex-vivo* and the levels of circulating Lp(a) in FH patients [91], (iii) there is no difference in Lp(a) clearance between wild-type and LDLR knockout mice, (iv) PCSK9i reduce Lp(a) in homozygote FH patients totally lacking

LDLR function [106], which can be explained by a direct effect of PCSK9 on Lp(a) assembly from apoB and apo(a) [89].

### **3. Kinetic determinants of plasma lipoprotein(a) concentrations *in vivo***

As referred to above, the plasma concentrations of Lp(a) have a strong heritable component related to genetic variations in the number of KIV<sub>2</sub> repeats, with epidemiological studies consistently demonstrating an inverse association between the size of apo(a) and plasma Lp(a) concentrations [5]. However, the precise impact of genetic variation in apo(a) on the dynamics of Lp(a) particles in the circulation remains unclear. Experimental data have suggested that the size of the apo(a) transcripts is inversely associated with hepatic *LPA* mRNA concentration [107], and by implication apo(a) production. On the other hand, Lp(a) with apo(a) isoforms of different sizes may have different binding affinities for the LDLR or other receptors [73]. Lp(a) particles with larger isoform size have also been shown to be more effectively removed via LDLR independent pathways [73]. Hence, data from these experimental studies generally suggest that smaller apo(a) isoforms are more efficiently secreted into the circulation, and to a lesser extent that their hepatic clearance may be impaired.

Accordingly, in healthy normolipidemic subjects, those with smaller apo(a) isoforms (ie, KIV repeats  $\leq 22$ ) had significantly higher apo(a) production rates (PR) and reduced apo(a) FCR compared with those with larger apo(a) isoform sizes [105]. Also, apo(a) PR and apo(a) isoform size, but not apo(a) FCR, were shown to be significant predictors of plasma apo(a) concentration. In another tracer study, patients with elevated Lp(a) concentrations had smaller apo(a) isoform sizes and higher apo(a) PR than patients with normal Lp(a) concentration [108], the FCR of Lp(a)-apo(a) not differing significantly between the groups; there was also a direct association between the concentration and PR of apo(a) in the groups with both elevated and normal Lp(a) concentration. Hence, these observations reinforce the proposition that plasma concentrations of Lp(a) are primarily determined by the rates of production and not clearance, and support the clinical use of agents that target the hepatic production and secretion of Lp(a).

### **4. Mechanism of action of therapeutic lowering of lipoprotein(a)**

Several therapeutic interventions, such as niacin, PCSK9 inhibitors, cholesteryl ester transfer protein (CETP) inhibitors and apoB antisense oligonucleotides, have been shown to significantly lower plasma Lp(a) concentration (discussed in another review of this series [109]). The associated mechanisms of action can elucidate the metabolism of Lp(a). Statins

have no impact, or may even increase plasma Lp(a) concentrations: a recent meta-analysis showed that statins (atorvastatin 10 mg/day and 80 mg/day, pravastatin 40 mg/day, rosuvastatin 40 mg/day, and pitavastatin 2 mg/day) significantly increased plasma Lp(a) concentrations [78]. This is supported by experimental data in HepG2 cells showing a higher *LPA* mRNA level in response to atorvastatin [78]. However, we demonstrated that atorvastatin (80 mg daily) did not significantly alter the FCR or PR of Lp(a)-apo(a) in healthy normolipidemic subjects.

#### **4.1 Niacin**

Niacin is one of few agents that can significantly lower plasma Lp(a) concentrations. Experimental data suggest that niacin decreases the expression of *LPA* mRNA [110]. This is consistent with a kinetic study showing that niacin lowered apo(a) concentration by decreasing the production of apo(a) in non-diabetic, obese and hypertriglyceridaemic men [111]. The lowering of the PR of Lp(a)-apo(a) by niacin was confirmed in another kinetic study in statin-treated patients with elevated Lp(a) [112].

#### **4.2 PCSK9 inhibitors**

Inhibition of PCSK9 with monoclonal antibodies (mAbs) can similarly lower plasma Lp(a) concentration. The role of PCSK9 in Lp(a) metabolism may predominantly involve regulation of the LDL receptor [86], but there is also evidence that PCSK9 may control the hepatic secretion of apo(a) [32,89]. In a recent kinetic study of healthy normolipidemic men, we found that 8-week treatment with Evolocumab significantly decreased plasma Lp(a) concentration chiefly by reducing the PR of Lp(a)-apo(a) particles with no effect on the corresponding FCR [52]. This effect is consistent with a tracer study conducted in non-human primates in which Alirocumab decreased the production of Lp(a)-apo(a) [94]. The reduction in Lp(a)-apo(a) PR with PCSK9 mAbs is supported by the *in vitro* studies mentioned above showing that PCSK9 induces Lp(a) intracellular assembly and secretion whereas PCSK9 mAbs reduce the extracellular release of Lp(a) [89].

By contrast to monotherapy, PCSK9 inhibition with Evolocumab lowered plasma Lp(a) concentration by increasing the FCR of Lp(a) in combination with high-dose atorvastatin [52]. However, the PR of Lp(a) was not significantly altered with the combination. Similar results were reported in a recent kinetic study of statin-treated patients with high Lp(a) [113]. In the latter study, 12-week treatment with Alirocumab significantly decreased plasma Lp(a) concentration chiefly by accelerating the FCR of Lp(a)-apo(a) particles with no effect on the corresponding PR [113]. Paralleling the findings of experimental and human studies

investigating the role of the LDLR in mediating Lp(a) uptake (reviewed in section 2.3), this effect of PCSK9 mAbs in combination with a high potency statin indicates that the LDLR likely plays a significant role in mediating Lp(a) clearance only when its expression is markedly upregulated and when LDL plasma levels are substantially lowered, allowing decreased competition between LDL and Lp(a) for receptor mediated uptake.

#### **4.3 CETP inhibitors**

CETP facilitates the transfer of cholesteryl ester from HDL to apoB-containing lipoproteins. Treatment with CETP inhibitors, either alone or in combination with statin, can lower Lp(a) concentrations by 20-25% [114]. The mechanism of action of CETP inhibition has been studied in patients with mild hypercholesterolemia. Using stable isotopes, Thomas *et al.* found that the CETP inhibitor Anacetrapib lowered Lp(a) concentration by reducing the PR of apo(a), without altering apo(a) catabolism [115]. However, the underlying mechanism for the reduction in Lp(a) production remains unclear and merits further investigation [114,115].

#### **4.4 ApoB antisense oligonucleotides**

The availability of apoB100 substrate plays a key role in the assembly and secretion of apoB100 containing particles in the liver, including VLDL and possibly Lp(a) particles. Accordingly, mipomersen, an antisense oligonucleotide that inhibits apoB synthesis, has been shown to significantly lower plasma concentrations of LDL, apoB and Lp(a). In a kinetic study of healthy volunteers, mipomersen decreased plasma Lp(a) levels by increasing the FCR of Lp(a) with no significant change in PR [116]. It is noteworthy that the increase in Lp(a) FCR observed was similar to the 30% increase in the FCR of LDL apoB100, supporting a role for the LDLR or related receptors in the clearance of Lp(a) particles. But given the well-recognized inhibitory effect of mipomersen on apoB synthesis, the lack of a significant effect on the PR of Lp(a) as well as VLDL apoB [116] appears paradoxical, particularly noting that knocking down apoB with siRNA actually reduces Lp(a) cellular secretion *in vitro* [32].

In aggregate, both niacin and PCSK9 mAbs are the only currently available and effective agents that lower plasma Lp(a) concentrations. Further mechanistic studies of the effect of CETP inhibitors and apoB antisense oligonucleotides on the metabolism of Lp(a) are warranted. Collectively, the aforementioned therapeutic interventions do not lower Lp(a) concentrations to levels that would theoretically mitigate the adverse effects of elevated Lp(a) on ASCVD [117,118]. However, clinical outcome trials in patients at high risk of ASCVD indicate that

some of the cardiovascular benefit of PCSK9 mAbs are mediated by the lowering of Lp(a) independently of the concurrent reduction in other atherogenic lipoproteins [119,120]. More potent Lp(a) lowering agents are however required to produce more drastic clinical impact. This can only at present be achieved with RNA-based therapies targeting apo(a) [121]. Lipoprotein apheresis acutely lowers Lp(a) by up to 70% by accelerating the clearance of Lp(a) particles. In studying the rebound of Lp(a) and LDL particle concentration following lipoprotein apheresis, we demonstrated that the clearance of Lp(a) is significantly slower than that of LDL-apoB in patients with elevated Lp(a) and ASCVD [122]. These findings suggest that the clearance pathways for Lp(a) differ from those of LDL-apoB. Other therapies such as selective thyroid hormone receptor agonists (such as Resmetirom) can effectively lower plasma Lp(a) concentrations. Activation of thyroid hormone receptor has been shown to increase *LDLR* expression, resulting in reduced circulating LDL particles [123]. However, the mode of action of thyroid hormone receptor agonists on Lp(a) metabolism remains unclear and merits further investigation.

## **5- Conclusion: gaps in knowledge**

While we have extensively reviewed the entire body of experimental and human evidence investigating the intracellular assembly, production, and catabolism of Lp(a), future research is still needed to understand whole body metabolism of Lp(a) (**FIGURE 4**). Major gaps in knowledge remain and the identification of the mechanistic processes governing both Lp(a) biology and metabolism is clearly required. These include further evidence to understand the stability of the covalent bonding between apo(a) and apoB100, the potential recycling of apo(a) in the circulation, the possible formation of Lp(a) complexes with triglyceride-rich lipoproteins, and the determination of the relative roles of hepatic and renal receptors in the clearance of Lp(a) particles. The role of oxidized phospholipids and other lipidomic and proteomic markers on Lp(a) metabolism also merits to be investigated further [124,125]. The post-absorptive and postprandial effect of classic lipid-regulating agents (e.g. fibrates and high dose fish oil supplementation) and other non-antibody approaches targeting PCSK9 (e.g. RNA therapeutics, adnectins, small molecules, and vaccination) on Lp(a) metabolism remain to be investigated. Further studies are also required to characterize the mode of action of antisense oligonucleotides or small interfering RNAs targeting apo(a) production on the metabolism of Lp(a) and other apoB100 containing lipoproteins against a background of statin therapy. Understanding the metabolism of Lp(a) is essential for developing new therapies and utilizing currently available

treatment to improve the ASCVD outcomes in patients with elevated Lp(a). Knowledge of the mode of action of therapeutic interventions is also important for informing shared-decision making and improving adherences to therapies.

**Declaration of competing interests**

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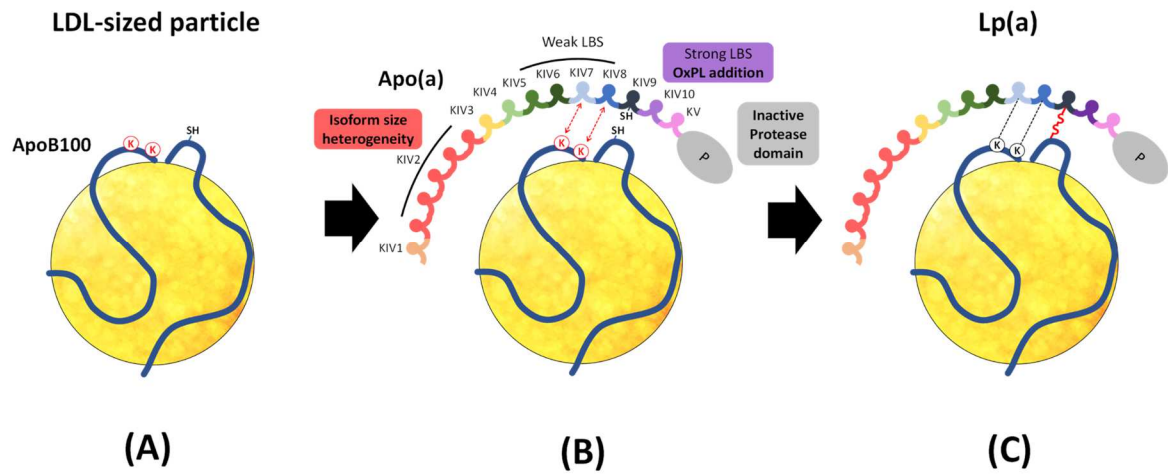
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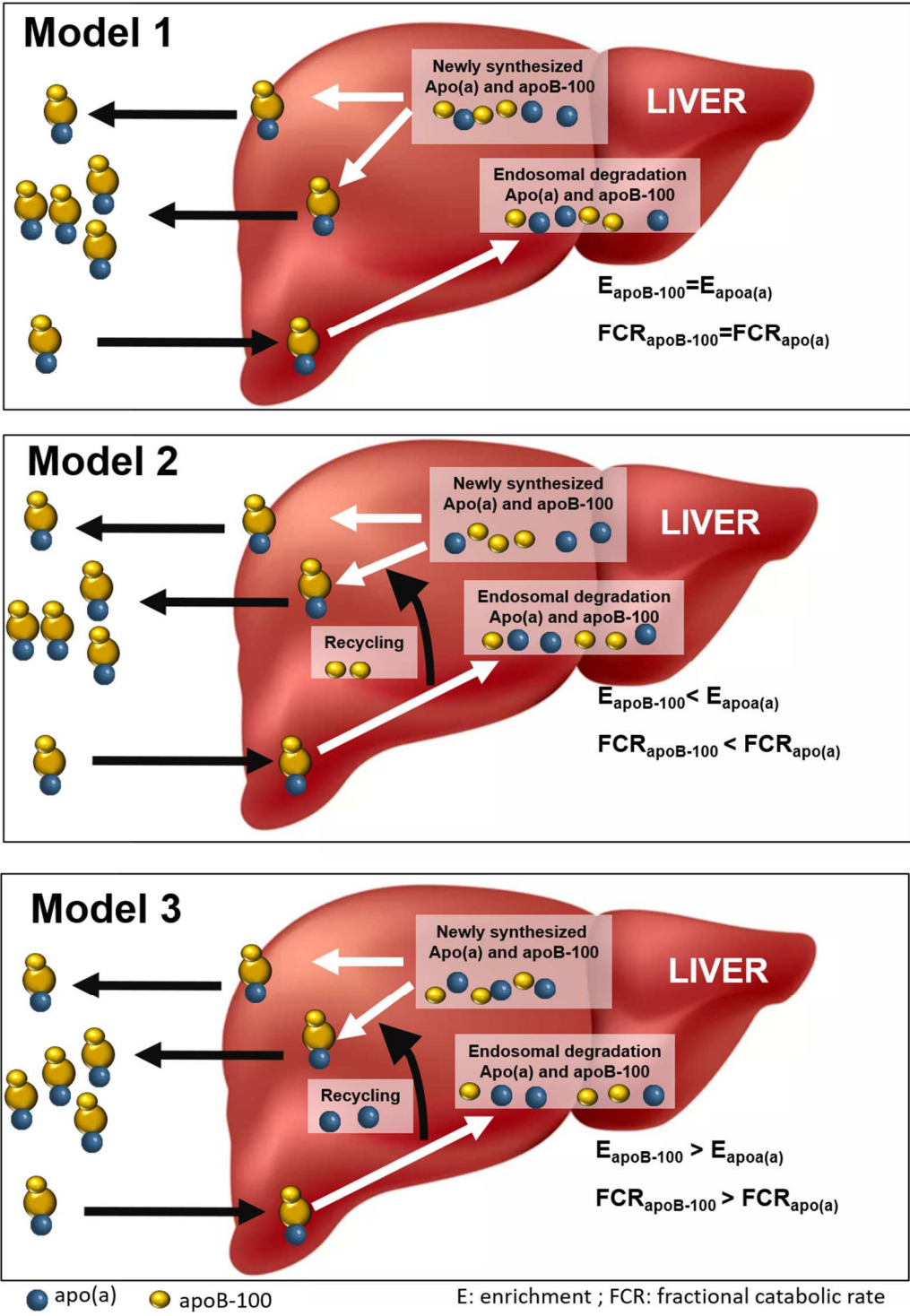
**FIGURE 1** - Schematic representation of two step Lp(a) assembly.

(A) Positioning of pre-cursor LDL-sized particle. (B) Non-covalent interactions between weak lysine binding site on the KIV<sub>7</sub> and KIV<sub>8</sub> and lysine residues (K) on apoB100. (C) Stabilization of Lp(a) particles by the formation of a disulphide bond between the free Cys<sub>4057</sub> on apo(a)-KIV<sub>9</sub> and Cys<sub>4326</sub> of apoB100.



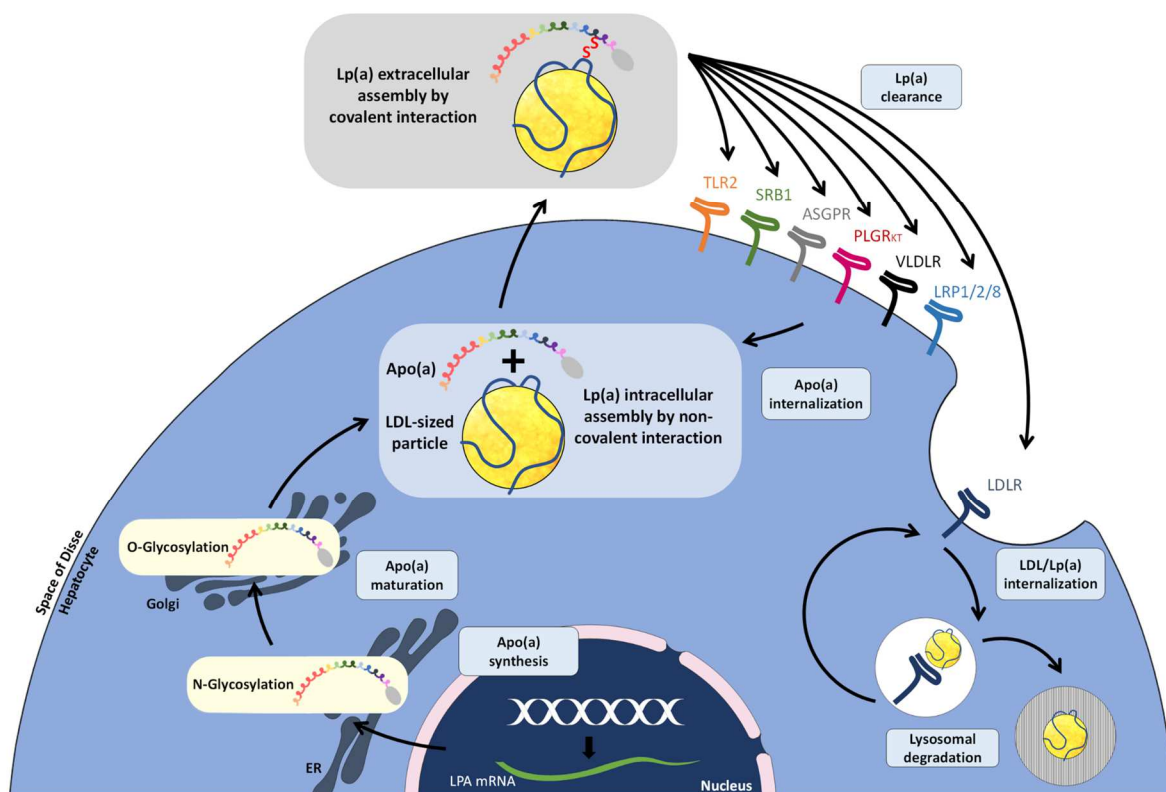
**FIGURE 2** – Hypothetical kinetic models describing the metabolism of apo(a) and apoB100 protein components of Lp(a) particles (adapted from [51]).

In Model 1: Lp(a) particles are assembled within or at the surface of hepatocytes; Model 2: apoB100 and apo(a) combine to form Lp(a) within or at the surface of hepatocytes; apo(a) is degraded and some apoB100 is recycled to the Lp(a) assembly site after a circulating Lp(a) is taken up by the liver; Model 3: apoB100 and apo(a) combine to form Lp(a) within or at the surface of hepatocytes; apoB100 is degraded whereas a proportion of apo(a) is recycled to the Lp(a) assembly site after a circulating Lp(a) is taken up by the liver.



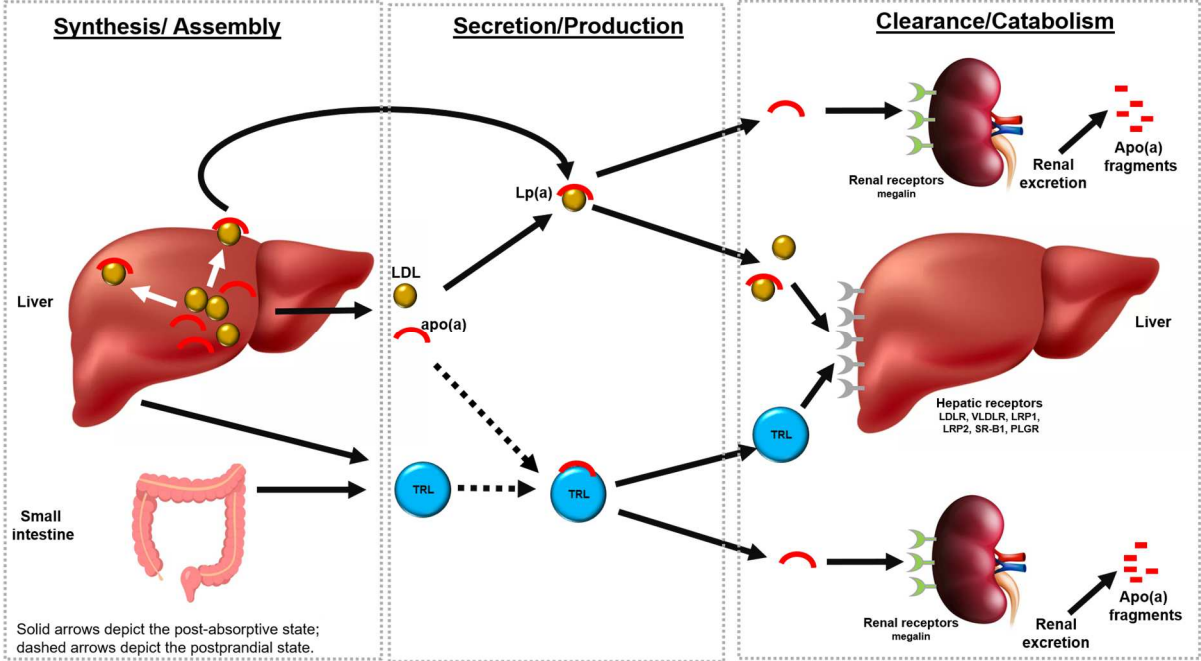
**FIGURE 3** – Synthesis, secretion, assembly, clearance and catabolism of lipoprotein(a) are centred on the liver.

Lp(a) production by hepatocytes is regulated at the apo(a) transcriptional and translational levels, at the protein maturation levels (including N- and O-glycosylation in their respective compartments), as well as at the Lp(a) assembly and secretion levels. Lp(a) assembly results from the non-covalent association of apo(a) with the apoB100 moiety of an LDL-sized particle intracellularly followed by their covalent attachment after secretion at the cell surface. Lp(a) plasma clearance is chiefly determined by the hepatic uptake of Lp(a). Several receptors have been proposed to mediate Lp(a) internalization such as the Toll like receptor 2 (TLR2), the Scavenger receptor class B type 1 (SRB1), the Asialoglycoprotein receptor (ASGPR), the Plasminogen receptor (PLGR<sub>KT</sub>), the VLDL receptor (VLDLR), the Lipoprotein receptor related proteins 1, 2 and 8 and the LDL receptor (LDLR). After endocytosis, Lp(a) has been proposed to undergo degradation in the lysosome. Alternative evidence advocates for selective uptake of free apo(a) by the ASGPR or recycling of apo(a) following endocytosis to serve as precursors of novel Lp(a) particles.



**FIGURE 4.** Whole body metabolism of Lp(a) involving the liver, small intestine, circulation and kidneys.

The pathways depicted refer to (A) synthesis and/or assembly of LDL and triglyceride-rich lipoproteins (TRLs), (B) secretion and/or production of Lp(a), (C) clearance and/or catabolism of Lp(a) by liver and kidneys. Some of these pathways are hypothetical constructs that require verification.

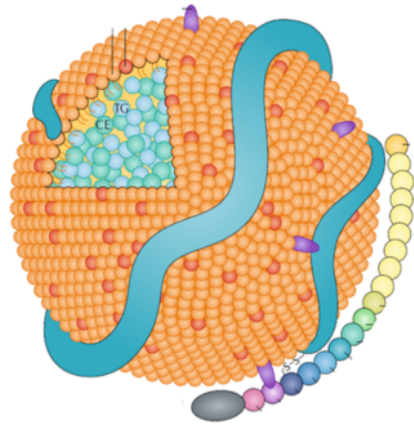


What determines plasma Lp(a) levels?

Niacin, PCSK9i, antisense  
oligo and siRNA

Apo(a) biosynthesis, secretion  
Lp(a) assembly

Lipoprotein (a)  
Hepatic capture



Plasminogen homology  
Antifibrinolytic properties

Cholesterol Deposition  
Atherosclerosis

oxPL and vascular  
inflammation

How does Lp(a) contribute to vessel disease ?