

脂蛋白(a)在冠状动脉粥样硬化性心脏病中的研究概述

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摘 要

脂蛋白(a) [Lipoprotein(a), Lp(a)]早在20世纪60年代被发现, 它是一种拥有独特结构和功能的脂蛋白, 其在血浆中的浓度主要受个体遗传因素的影响。随着不断深入的研究, 人们逐渐意识到Lp(a)在心血管疾病(Cardiovascular Disease, CVD)中的重要作用, 并开始关注如何有效地降低Lp(a)水平, 来减少心血管事件的发生。Lp(a)具有促炎、抗纤溶和促进动脉粥样硬化等特点。本文旨在介绍Lp(a)的组成、分子结构以及生理功能, 阐述其在动脉粥样硬化中的作用机制, 并探讨降低Lp(a)水平的新兴且更有效的治疗方案。

关键词

脂蛋白(a), 动脉粥样硬化性心血管疾病, 降低脂蛋白(a)的疗法

Overview of the Study of Lipoprotein(a) in Atherosclerotic Cardiovascular Disease

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Abstract

Lipoprotein(a) [Lp(a)] was discovered as early as the 1960s. It is a lipoprotein with a unique structure and function, and its concentration in plasma is mainly influenced by individual genetic factors. With continuous in-depth research, people gradually realize the important role of Lp(a) in

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cardiovascular disease (CVD) and begin to pay attention to how to effectively reduce Lp(a) levels to reduce the occurrence of cardiovascular events. Lipoprotein a [Lp(a)] has the characteristics of promoting inflammation, anti fibrinolysis and promoting atherosclerosis. The purpose of this article is to introduce the composition, molecular structure and physiological function of lipoprotein(a), elaborate its mechanism of action in atherosclerosis, and explore a new and more effective treatment scheme to reduce the level of Lp(a).

Keywords

Lipoprotein(a), Atherosclerotic Cardiovascular Disease, Treatment to Reduce Lipoprotein(a)

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1. 引言

冠状动脉粥样硬化性心脏病简称冠心病(Coronary heart disease, CHD), 是全球患者发病与死亡的主要原因之一, 其病理本质是动脉粥样硬化的发生与发展。长期以来, 低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)被视为动脉粥样硬化进展的关键致病因子, 并成为降脂治疗的基石。然而, 即便对 LDL-C、血压、血糖等传统危险因素进行严格管理, 仍有相当一部分患者存在残余心血管风险。近年来, Lp(a)作为一项遗传主导的独立危险因素逐渐受到重视。本文旨在系统阐述 Lp(a)在冠心病中的作用及其临床意义。首先, 本文将重点阐述 Lp(a)独特的分子结构及病理功能, 说明其在动脉粥样硬化进程中的作用机制, 同时探讨 Lp(a)与冠心病风险的遗传及流行病学关联, 阐述临床检测标准化现状与挑战, 最后, 通过分析不同作用机制的降脂疗法对 Lp(a)水平的影响及疗效限度, 并展望新兴治疗方案的潜力与未来研究方向。本文希望为 Lp(a)的深入研究及临床干预提供清晰的框架。

2. Lp(a)的结构

脂蛋白(a)于 1963 年由挪威遗传学家 Berg [1]首次发现, Lp(a)是一种肝脏合成的独立的脂蛋白, 并不是直接由极低密度脂蛋白(very low density lipoprotein, VLDL)转化而来。Lp(a)是一种与载脂蛋白(a) [apolipoprotein a, Apo(a)]结合的低密度脂蛋白(low density lipoprotein, LDL)胆固醇样颗粒。Lp(a)主要是由低密度脂蛋白、Apo(a)和载脂蛋白 B-100 (apolipoprotein B, ApoB)组成的特殊蛋白, 其中 Apo(a)和 ApoB 通过二硫键相连[2]。

Lp(a)的生理功能主要是因为 Apo(a)亚基的存在。Apo(a)含有一个名为“kringle”的独特蛋白质结构域, 这主要由 80 个氨基酸组成[3]。Apo(a)含有 10 种不同类型的纤溶酶原样 kringle IV 结构域(KIV), 由 KIV1 的 1 个拷贝、KIV2 的多个拷贝和 KIV3-10 的 1 个拷贝以及一个 kringle V 结构域和一个失活的蛋白酶结构域组成。除了 kringle IV 型 2 (KIV2)外, 所有 KIV 结构域都以单拷贝的形式存在[4]。Apo(a)亚型的大小是根据 Apo(a)基因中 KIV2 重复编码序列的数量来决定的[5] [6], 且 Apo(a)的大小通常与 Lp(a)浓度成反比。较大的 Apo(a)颗粒在肝细胞内加工时间延长和更大颗粒在细胞内降解时间增加, Apo(a)颗粒大小与肝脏的产生率呈负相关[7]。因此, Apo(a)颗粒大小与免疫比浊法测量的 Lp(a)血浆浓度呈负相关, 即高浓度 Lp(a)以小颗粒型为主, 而低浓度 Lp(a)以大颗粒型为主[7] [8]。KIV2 重复序列越少, Apo(a)大小越小, Lp(a)水平越高, 因为肝细胞可以以更高的速率产生更小的 Apo(a)颗粒[9]。

3. Lp(a)的测量及标准化

个体 Lp(a)浓度在整个生命周期中相对稳定, 在一般人群中范围为<1 至>200 mg/dL [10]。由于血浆 Lp(a)浓度主要由遗传决定, 因此几乎没有检测到饮食和环境的影响, 并且整个生命周期的浓度变化不大 [11][12]。出生后第 7 天, 循环血浆 Lp(a)水平升高, 在出生后几个月内可达到恒定浓度 [13]。因此, Lp(a)可能只需要测量一次, 除非怀疑有继发性原因或采取特殊治疗以降低其血浆浓度。英国心脏协会采用了正在进行的哥本哈根普通人群研究的数据 [14], 根据百分位数分布对这种风险进行了分级: 32~90 nmol/L 为轻微; 90~200 nmol/L 为中等; 200~400 nmol/L 为高; >400 nmol/L 为非常高。英国心脏协会建议在以下人群中测量 Lp(a): 1. 有过早动脉粥样硬化性心血管疾病的个人或家族史(<60 岁)。2. 血浆 Lp(a)浓度高(>200 nmol/L)者的一级亲属。3. 家族性高胆固醇血症(Familialhypercholesterolemia, FH), 或其他遗传形式的血脂异常。4. 钙化性主动脉瓣狭窄。5. 10 年心血管事件的危险增加(但<15%) [15]。

研究发现, Lp(a)浓度因种族或民族而异, 不同人群之间的 Lp(a)血浆水平存在差异, Lp(a)在中国人、白人、和南亚人中浓度偏低, 而在黑种人中浓度最高 [16]。值得注意的是, 有些研究发现在某些种族和族裔群体中, Lp(a)升高与冠心病风险增加的关联并不一致, 特别是在非洲血统的人群中, 数据存在矛盾 [17]-[19], 这种差异的病理生理基础尚不确定, 值得进一步研究。此外, 女性的 Lp(a)水平变异更大, 通常在更年期期间升高。一项研究显示, 绝经后女性的 Lp(a)水平增加了 27%, 而在激素替代治疗期间水平 Lp(a)降低了 12% [20]。

由于 Lp(a)的大小变化很大, 并且主要由 Apo(a)的大小决定, 决定血液 Lp(a)水平的主要遗传因素是 LPA 基因中编码 KIV 重复序列数量的拷贝数差异。KIV 型 2 结构域重复序列的数量决定了 Apo(a)同构体的大小, 且与 Lp(a)浓度成反比, 所以准确测量 Lp(a)是一项重大挑战 [21]。Lp(a)最合适的测量单位是以摩尔单位测量(nmol/L) [22], 但存在相当大的困难 [23], 因此, 在临床应用中常用质量单位(mg/dL)进行测量 [24][25]。不建议把 Lp(a)浓度从 mg/dL 转换为 nmol/L, 因为由于每种基于免疫测定的分析方法对异构型的依赖性不同, 质量尺度和摩尔尺度之间没有一致的转换因子 [25][26]。虽然目前质量测量存在局限性, 但以质量单位检测方法更受欢迎, 还可以促进心血管疾病风险分层 [24], 尤其是在高风险人群中。

4. Lp(a)与心血管疾病

脂质紊乱大致可以分为 4 个“临床”类别: 低密度脂蛋白胆固醇升高、高密度脂蛋白胆固醇降低、甘油三酯升高和 Lp(a)升高。在当今的基因时代, 显然只有载脂蛋白 B-100 含量升高的脂蛋白[极低密度脂蛋白、中密度脂蛋白、LDL-C、Lp(a)]才与心血管风险增加有因果关系。在临床层面, Lp(a)升高是这 4 种脂质紊乱中研究较少的 [27]。在各种与冠心病相关的脂蛋白异常中, Lp(a)在冠心病的发生和发展中的作用重新引起了人们的兴趣。

Clarke R 等人在研究中发现有三个染色体区域(6q26-27、9p21 和 1p13)与冠心病风险密切相关。6q26-27 上编码 Lp(a)的 LPA 基因座关联性最强。他们在 LPA 基因座上发现了一个常见变异(rs10455872), 冠心病比值为 1.70 (95% 置信区间 CI, 1.49 至 1.95), 另一个独立变异(rs3798220)的比值为 1.92 (95% CI, 1.48 至 2.49)。这两个变异都与 Lp(a)水平升高、LPA 拷贝数减少(决定 kringle IV 型 2 重复序列的数量)和 Lp(a)体积较小密切相关。从而确定了两种 LPA 变异体, 它们与 Lp(a)水平升高和冠心病风险升高有着密切的关系 [28]。还有研究发现, Lp(a)基因座(rs10455872)中的一个单核苷酸多态性(SNP)与多个种族的主动脉瓣钙化以及临床主动脉瓣狭窄的发生有关 [29]。

在一项孟德尔随机化分析中, 揭示了 Lp(a)水平与冠心病、主动脉瘤、大动脉粥样硬化中风之间存在因果关系 [30], 在调整长期平均血脂水平和其他已确定的危险因素后, 这些相关性仅稍有降低, 因此增加

了 Lp(a)是冠心病独立危险因素的可能性。最新研究结果显示, 较高浓度的 Lp(a)对心肌梗死(Myocardial infarction, MI)和主动脉瓣狭窄风险影响最大, 而对缺血性卒中、周围动脉疾病、心力衰竭、心血管疾病死亡率及整体死亡率的影响显著却略弱于前者[31]-[33]。

先前的几项大规模心血管结局试验的事后分析发现, 尽管 LDL-C 大幅降低, Lp(a)浓度仍与剩余心血管风险相关[34]-[36]。研究发现, 当 LDL-C 低于 104 mg/dl 时, Lp(a)已成为公认的心血管疾病危险因素, Lp(a)与心血管疾病的相关性比 LDL-C 更密切, 并且是心血管疾病的残留危险因素[37]。Kamstrup P.R.观察到 MI 风险随 Lp(a)水平升高也逐步增加, Lp(a)水平可预测一般人群 MI 风险增加 3~4 倍[38]。一项前瞻性观察性研究观察了观急性 ST 段抬高型心肌梗死患者在四个时间点 Lp(a)水平的变化。Lp(a)中位数从入院时的 7.9 mg/dL 升至次日的 8.4 mg/dL, 第二天升至 9.3 mg/dL, 并在出院后随访时达到 11.2 mg/dL [39]。在 MI 患者中, 高 Lp(a)水平也可提高主要不良心血管事件(MACE)发生率[40]。一项荟萃分析表明, 无论在普通人群还是心血管疾病患者中, 其中的 Lp(a)水平都显著增加了全因死亡率和心血管死亡风险[41]。

5. Lp(a)介导 CVD 的机制

Lp(a)通过多种机制来增加 CVD 风险。Lp(a)的致动脉粥样硬化作用大致可以分为 3 类: 促动脉粥样硬化、促炎和潜在抗纤维蛋白溶解。由于 Lp(a)在结构上具有 LDL 颗粒, 因此也具有 LDL 颗粒所有致动脉粥样硬化风险, 包括其进入血管壁后易于氧化, 从而产生高度免疫原性和促炎性的氧化 LDL [42]。值得注意的是, 动力学研究指出 Lp(a)颗粒在血管壁上的优先积累, 这可能增加 Lp(a)与低密度脂蛋白胆固醇的致动脉粥样硬化潜力[43]。

Lp(a)与冠状动脉硬化的严重程度独立相关, 通过增加碱性磷酸酶(ALP)活性和上调前钙化蛋白(如骨形态发生蛋白-2 (BMP2)和骨质素(OPN)来促进血管钙化[44]-[46]。不仅如此, 在等摩尔基础上, Lp(a)比 LDL-C 更具有致动脉粥样硬化性, 因为根据 Lp(a)的结构, 它不仅包含 LDL 的所有促动脉粥样硬化成分, 还包含 Apo(a)。Apo(a)通过其他机制增强动脉粥样硬化血栓形成, 包括通过其氧化磷脂(oxidized phospholipid, OxPL)含量引起炎症、存在赖氨酸结合位点导致其在动脉壁中积聚、以及通过抑制纤溶酶原活化产生潜在的抗纤溶作用[47]。Apo(a)含有赖氨酸结合位点, 使其能够紧密结合到裸露内皮的暴露表面上, 进入并积聚在内膜下空间或主动脉瓣叶中, 从而导致炎症。体外和动物研究表明, Lp(a)具有相似的 kringle 结构和失活的蛋白酶区, 通过竞争性抑制纤溶酶的激活和功能来抑制纤维蛋白溶解, 从而最终促进血栓形成[48][49]。然而, 目前尚不清楚这种竞争性抑制机制在人体内是否有效, 因为纤溶酶原通常存在大量摩尔过量的 Lp(a)。

Lp(a)中的 OxPL 成分可存在于 Lp(a)的脂质相中, 也可与 Apo(a)共价结合[50][51], 具有促炎的作用, 并赋予 Lp(a)多种促动脉粥样硬化特性。作为氧化磷脂的载体, Lp(a)还可以激活免疫细胞和炎症通路, 如 Toll 样受体、白介素 6 (IL-6)、IL-1 β 和 NF- κ B 信号通路, 从而加剧动脉壁炎症并影响内皮细胞功能[52]。在一些研究中, Lp(a)上的 OxPL 还上调了炎症基因, 并诱导了白细胞介素 8 [53]和单核细胞趋化蛋白 1 [54]的释放。根据评估临床终点的研究, 已经证明 Lp(a)和 MACE 之间的关系被全身性炎症标志物修饰, Lp(a)较高和 C 反应蛋白较低的患者 MACE 明显低于 Lp(a)较高和 C 反应蛋白较高的患者[55]。

6. 降低 Lp(a)水平的方法

6.1. 生活方式的干预

Lp(a)主要受遗传因素的影响, 生活方式的改变对降低 Lp(a)浓度的作用很小, 而且缺乏对照试验的证据, 很难评估对结果的影响是否可以单独归因于 Lp(a)的降低, 或者还存在其他伴随因素[56]。但有专家认为治疗性生活方式干预仍然是控制 Lp(a)水平的基础, 通过改变生活方式, 如增加体育活动或采用健康

饮食, 可能也会对 Lp(a)值产生积极影响[25]。

6.2. HMG-CoA 还原酶抑制剂(他汀类药物)

他汀类药物是 3-羟基-3-甲基戊二酰辅酶 A (HMG-CoA)还原酶的竞争性抑制剂, 可影响胆固醇合成的限速步骤, 抑制 HMG-CoA 还原酶可增加肝脏 LDL 受体的表达, 从而导致循环中 LDL-C 水平降低。目前他汀类药物仍然是 ASCVD 一级预防最有效、最安全的药物类别之一, 但是关于他汀类药物对 Lp(a)水平影响的研究结果不太一致[57], 其影响似乎与 Apo(a)异构体有关。JUPITER 研究[34]表明, 在使用他汀类药物后, 可以使 Lp(a)水平有轻度的升高。然而, 即使应用他汀类药物后 Lp(a)略有增加, 但也无临床显著性[58]。与其他他汀类药物相比, 匹伐他汀似乎对 Lp(a)水平具有中性影响, 甚至可能略微降低, 不过, 这一点仍需确认[59]。

6.3. 烟酸

烟酸类药物是 B 族维生素的一种, 它通过降低细胞内环磷酸腺苷(cAMP)的水平, 来抑制脂肪组织内激素敏感脂肪酶的活性, 导致甘油三酯分解产生游离脂肪酸减少, 导致肝脏合成脂质降低, 极低密度脂蛋白胆固醇的合成和释放减少, 从而使 LDL-C 来源减少。经研究表明, 烟酸也可减低 Lp(a)水平, 但是存在副作用。HPS2-THRIVE [60]和 AIM-HIGH [61]在研究中发现, 烟酸可使 Lp(a)水平降低达 30%, 但不能显著降低主要血管事件的风险, 反而却显著增加了严重不良事件的风险。

6.4. 前蛋白转化酶枯草杆菌蛋白酶/Kexin9 型(PCSK9)抑制剂

PCSK9 抑制剂是一种丝氨酸蛋白酶, 属于前蛋白转化酶家族, 主要由肝脏产生[62]。外周细胞从循环中摄取胆固醇以 LDL 受体(low-density lipoprotein receptor, LDLR)为主, 约 75%的循环胆固醇由 LDLR 降解。PCSK9 抑制剂通过阻断 PCSK9 蛋白介导的 LDLR 降解过程, 上调细胞表面 LDLR 水平最终达到降低 LDL 的作用。PCSK9 抑制剂既能增加分解代谢, 也可以降低 Lp(a)的产生[63]。目前主要有两种药物: 依洛尤单抗(Evolocumab)和阿里库单抗(Alirocumab)。在 FOURIER 和 ODYSSEY 的研究中, PCSK9 抑制剂降低了 Lp(a)水平: 依洛尤单抗平均降低 29.5% [64] [65], 阿里库单抗平均降低 23.5% [66]。依洛尤单抗可以显著降低 Lp(a)水平, 对于基线 Lp(a)水平较高的患者, 从 PCSK9 抑制中获得的益处更大[10]。

6.5. RNA 干扰疗法

RNA 干扰(RNA interference, RNAi)疗法是降低 Lp(a)水平的新型治疗方法, 通过小干扰 RNA (small interfering RNA, siRNA)或反义寡核苷酸(Antisenseoligonucleotides, ASO)与靶 mRNA 序列特异部位结合并降解靶 mRNA, 沉默与 Lp(a)合成、转运和吸收相关蛋白基因的表达, 最终降低血液 Lp(a)水平[67]。在 Sotirios Tsimikas 等人的研究中证实 ISIS-APO(a)Rx 在降低 Lp(a)方面有好的效果, 但 ISIS-APO(a)Rx 在减少心血管事件和钙化主动脉瓣狭窄方面的有效性还需要进一步的临床试验来证明[68]。Olpasian 是一类最早的, 合成的, 双链的 N-乙酰半乳糖合成的小干扰 RNA (siRNA), 通过直接抑制肝细胞中的 LPA 信使 RNA 的转化, 并能有效降低血浆 Lp(a)浓度 71%~97% [69]。目前已进入临床前期试验阶段的第二代反义寡核苷酸药物 Pelacarsen, 通过结合并诱导核糖核酸酶内切酶降解编码 Apo(a)的 mRNA 来降低 Lp(a), 在第二阶段的临床试验表明, Pelacarsen 可将 Lp(a)水平降低 80%, 而降低 Lp(a)水平是否可以降低 ASCVD 风险还需要进一步临床试验研究[70]。Mipomersen (米泊美生)是一种以载脂蛋白 B 为靶点的寡核苷酸, 通过靶向抑制 ApoB-100 的脂蛋白合成, 进而减少 Lp(a)水平, 有研究发现米泊美生可使 Lp(a)水平降低 20%~50% [71]。

6.6. 脂蛋白分离术

脂蛋白分离术(lipoprotein apheresis, LA)是目前能够显著降低 Lp(a)水平的方法,LA 可以降低含 ApoB-100 的脂蛋白[LDL-C 和 Lp(a)] [72]。单次治疗可使 LDL-C 和 Lp(a)水平降低约 60%~75%,但随后会很快升高[22] [73],因此必须定期重复行 LA。在 ASCVD 患者中, LA 可显著减少心血管事件[74]。LA 是首个获得美国食品药品监督管理局(FDA)初步批准用于 Lp(a) > 60 mg/dL (>150 nmol/L)患者,无论其基线 LDL-C 水平如何的 Lp(a)升高治疗方法[75]。对于 Lp(a)水平极高且 ASCVD 进展性的患者,尽管其他风险因素已得到最佳治疗,仍可考虑行 LA [25]。但是, LA 在临床广泛应用存在一些障碍,如耗时、价格昂贵等,导致其在应用中受到了一定限制[76]。

为更清晰地对比不同治疗策略的作用机制与临床证据,现将主要内容总结于表 1。

Table 1. Comparison of the mechanisms of action, efficacy characteristics, and clinical evidence of different Lp(a)-lowering therapeutic strategies

表 1. Lp(a)不同治疗策略的作用机制、疗效特征与临床证据比较

作用机制分类	代表药物/疗法	作用靶点	主要机制	Lp(a)降低幅度	临床试验阶段	对心血管结局的影响
抑制胆固醇合成	他汀类药物	HMG-CoA 还原酶	上调 LDL 受体, 对 Lp(a)合成影响小	0%至轻度升高(≤10%)	已上市(IV 期)	获益明确, 但源于 LDL-C 降低
减少 VLDL 合成	烟酸	激素敏感脂肪酶	减少 VLDL 合成与分泌	达 30%	III 期终止 (AIM-HIGH 等)	未显示额外心血管获益, 不良反应增加
增强 LDL 受体清除	PCSK9 单抗 (如依洛尤单抗)	PCSK9 蛋白	阻断 PCSK9 介导的 LDL 受体降解, 上调受体水平以促进清除	约 23%~30%	已上市(III 期结局试验完成)	明确降低心血管事件, Lp(a)降幅或与额外获益相关
靶向 ApoB 合成	米泊美生	ApoB-100 mRNA	反义寡核苷酸抑制所有含 ApoB 脂蛋白合成	20%~50%	已上市(限用)	长期心血管结局数据有限, 存在副作用限制应用
靶向 Apo(a) 合成	Pelacarsen (ASO)	Apo(a) mRNA	反义寡核苷酸诱导编码 Apo(a)的 mRNA 降解	80%	III 期进行中 (Lp(a)HORIZON)	待证实(尚无心血管结局数据)
	Olpasiran (siRNA)	Apo(a) mRNA	siRNA 介导 LPA mRNA 沉默, 抑制 Apo(a)蛋白合成	71%~97%	III 期进行中 (OCEAN(a)-OUTCOMES)	待证实(尚无心血管结局数据)
物理清除	脂蛋白分离术	含 ApoB 脂蛋白	体外直接清除血浆 Lp(a)	单次约 60%~75% (需定期进行)	临床应用 (用于难治性病例)	观察性研究显示可减少事件, 但缺乏 RCT; 可及性低

注: ASO: 反义寡核苷酸; siRNA: 小干扰 RNA; RCT: 随机对照试验。

7. 小结

综上所述, Lp(a)在冠状动脉粥样硬化性心脏病中扮演着不容忽视的角色, Lp(a)作为一项主要由 LPA 基因决定的独立风险因子, 通过促动脉粥样硬化、促炎及抗纤溶等多重机制直接参与疾病进程。然而, 传统降脂策略对其调控作用有限, 导致高 Lp(a)血症成为当前心血管残余风险的重要原因。值得关注的是,

以 PCSK9 抑制剂与 RNA 干扰技术为代表的新兴靶向疗法, 已展现出显著降低 Lp(a)水平的潜力, 然而这些干预措施对最终心血管预后的影响, 尚需心血管结局试验的进一步证实。在此背景下, 随着基因检测技术的普及与精准靶向药物的逐步成熟, Lp(a)有望从传统的风险标志物转化为可干预的临床靶点。通过系统性筛查高危人群并依据个体风险实施分层干预, Lp(a)或将成为优化心血管疾病防治体系、降低心血管残余风险的关键一环。

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