·文献综述·

脂质代谢在新生血管性年龄相关性黄斑变性进展及治疗中的作用

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摘要

新生血管性年龄相关性黄斑变性(nARMD)是一种普遍发生的、与年龄相关的严重影响患者视力的视网膜疾病。大量研究显示,脂质代谢紊乱在 nARMD 的进展中发挥着促进作用,而这种关系涉及到多个因素,包括脂肪酸、胆固醇、脂质代谢基因变异等。脂质代谢紊乱通过刺激氧化应激、抑制自噬,以及二者间的相互作用,引起了视网膜血管的异常和炎症反应,从而加速新生血管的形成,导致黄斑区细胞和组织的损伤。在动物实验中,开发针对脂质代谢紊乱的药物证实了通过调节脂质代谢是治疗 nARMD 的一种潜在有效策略。基于这一发现,文章对脂质代谢在 nARMD 进展及治疗中的作用进行综述,旨在为下一步的临床研究提供参考和依据,为 nARMD 的临床治疗开辟新的思路。

关键词:脂质代谢;新生血管性年龄相关性黄斑变性;氧化应激;自噬;脂质代谢相关药物治疗

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Role of lipid metabolism in the progression and treatment of neovascular age-related macular degeneration

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Abstract

• Neovascular age-related macular degeneration (nARMD) is a prevalent age-related retinal disease that significantly impairs vision. Numerous studies have shown that lipid metabolism disorders contribute to the progression of nARMD. The relationship is complex and involved factors such as fatty acids, cholesterol, variations in lipid metabolism genes, and other influencing factors. Lipid metabolism disorders lead to retinal vascular abnormalities and inflammatory responses by triggering oxidative stress and inhibiting autophagy. This, in turn, accelerates the formation of new blood vessels and causes damage to macular cells and tissues. In animal experiments, drugs designed for lipid metabolism disorders have shown that regulating lipid metabolism could be a potentially effective strategy for treating nARMD. This article reviews the role of lipid metabolism in the progression and treatment of neovascular age-related macular degeneration, aiming to offer new insights for nARMD treatment.

• KEYWORDS: lipid metabolism; neovascular age-related macular degeneration; oxidative stress; autophagy; lipid metabolism-related drug therapy

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0 引言

年龄相关性黄斑变性(age-related macular degeneration, ARMD)是一种导致 55 岁以上人群视力损伤的重要疾病,随着人口老龄化,发病率逐年升高[1]。ARMD 可分为两型:萎缩型(非渗出性或干性 ARMD)占 ARMD 患者的 80%-90%,渗出型(新生血管性或湿性 ARMD)占 ARMD 患者的 10%-15%。虽然新生血管性年龄相关性黄斑变性(neovascular age-related macular

degeneration,nARMD)占比较少,但 nARMD 导致严重视力丧失的比例约为 90%[2]。目前抗血管内皮生长因子(vascular endothelial growth factor, VEGF)已被广泛运用 nARMD 治疗中。然而,阻断 VEGF 不但不能治愈 VEGF 造成的黄斑区视网膜病理变化,反而可能加重视网膜神经变性和血管损伤[3]。因此,开发侵袭性更小、更有效的治疗方法显得尤为重要。近期研究发现脂质升高可促进新生血管形成并加速 nARMD 进展,表明脂质代谢促进 nARMD 的进展[4]。本文对脂质代谢在 nARMD 进展及治疗中的作用进行综述。

1 ARMD 的病理研究进展

玻璃膜疣是 ARMD 进展过程中重要的病理特征。在早期和中期 ARMD,视网膜色素上皮(retinal pigment epithelium, RPE)和脉络膜之间积聚的富含脂质的沉积物,称为玻璃膜疣[5]。进展到 ARMD 晚期可分为萎缩型和渗出型,萎缩型病理特征是 RPE 和上覆的神经感觉层视网膜萎缩,称为地图样萎缩(geographic atrophy, GA),渗出型病理特征是新生血管性增生,即神经感觉层视网膜下的增殖性新生血管形成,也称为脉络膜新生血管形成(choroidal neovascularization, CNV)[6]。CNV 表现为病理性新生血管生长到黄斑区视网膜,新生血管的形成导致视网膜内层或视网膜下间隙出血和液体渗漏,反复的黄斑出血和渗出最终导致纤维化,造成了黄斑的形态和功能永久性的损害[7]。玻璃膜疣的具体组成在许多生化和组织学中进行了研究。这些研究表明,玻璃膜疣具有显著的脂质组成,所以脂质代谢异常可能是 ARMD 重要的发病机制[8]。

2 脂质代谢参与 nARMD 的病理过程

2.1 脂质代谢 脂质代谢的主要作用是将脂质输送到外周组织或将脂质输送回肝脏进行回收或清除。脂质代谢有 3 种主要途径:外源性、内源性和反向胆固醇转运途径。外源性途径主要处理膳食性脂质;内源性途径是肝脏合成的脂质加工过程;胆固醇反向转运是从组织中去除胆固醇并将其返回肝脏的过程[9]。生化研究显示玻璃膜疣主要由脂质组成,并且遗传学研究证实了与 nARMD 相关的脂质代谢相关基因存在多态性,已有研究报道在 nARMD 患者的血清脂蛋白谱中有显著的变化[8]。这些研究证实了脂质代谢参与 nARMD 的病理过程。

2.2 膳食补充 ω-3 LCPUFA 可能减缓 ARMD 进展到 nARMD 视网膜是人体脂质含量最高的组织之一[10]。光感受器外段(photoreceptor outer segment, POS)由一个含有蛋白质和脂质的光敏盘组成,包括磷脂(占总脂质的 90%-95%)和胆固醇(占总脂质的 4%-6%),在视网膜磷脂中,长链多不饱和脂肪酸(long-chain polyunsaturated fatty acid, LCPUFA)约占总磷脂的 45%[11]。高浓度的 LCPUFA 可以保持细胞膜的流动性,这是有效视觉转导的前提,也是视网膜维持正常功能的关键[12]。研究表明 ω-3长链多不饱和脂肪酸(ω-3LCPUFA)包括二十二碳六烯酸(docosahexaenoic acid, DHA)和二十碳五烯酸(eicosapentaenoic acid, EPA)可以通过抑制肿瘤坏死因子 α(tumor necrosis factor alpha, TNF-α)减少病理性新生血管生成[13]。ω-3LCPUFA 不能由人体自身合成,必须从饮食中获取[14]。Keenan 等[15]在年龄相关性眼病研究(The Age-Related Eye Disease Study, AREDS)和 AREDS2 研究回顾性分析发现严格坚持地中海饮食(富含鱼类和 ω-3 LC-PUFA)可以降低大玻璃膜疣和晚期 ARMD 发生的风险。AREDS 表明,ω-3 LCPUFA 摄入量较高的患者双侧玻璃膜疣发展为 GA 或 CNV 的可能性降低了 30%[16]。一项大型队列研究表明,ω-3 LCPUFA 血浆浓度较高的人群中 ARMD 的发病率比较低水平的患者低 42%[17]。细胞色素 P450(cytochrome P450, CYP)是一系列多样的酶,可催化许多药物和有机物质(包括脂质)的氧化,CYP 在 nARMD 患者的视网膜脂质沉积的积累和形成中发挥的作用,临床和实验研究表明,抑制 CYP2C 活性增加了膳食中 ω-3 LCPUFA 对抗病理性视网膜和 CNV 的作用[18-19]。另一项研究表明 CYP2J2 抑制剂增强了 ω-3 LCPUFA 对 CNV 的抑制作用[20]。然而另有研究发现膳食中补充 ω-3 LCPUFA 并不能减缓 ARMD 的进展或降低发生中度至重度视力丧失的风险[21]。关于膳食补充 ω-3 LCPUFA 能否减缓 ARMD 进展到晚期(GA 或 CNV)还需要进一步研究。

2.3 胆固醇代谢通过调节巨噬细胞活化来促进 nARMD 的进展 研究表明,胆固醇代谢是巨噬细胞活化的关键调节因子[9,22]。在 nARMD 病变中,已经证实了巨噬细胞是主要的细胞类型,巨噬细胞在 nARMD 的发病机制中起着至关重要的作用,巨噬细胞具有促炎和促血管生成的特性,研究表明抑制巨噬细胞向视网膜迁移可以抑制 CNV[23]。胆固醇代谢通过调节巨噬细胞活化来促进 nARMD 的进展。Sene 等[24]研究证明,在衰老的巨噬细胞中,受肝脏 X 受体(liver X-activated receptor, LXR)和 miR-33 调节的 ATP 结合盒转运子 A1(ATP-binding cassette transporter A1, ABCA1)表达降低的影响,损害了细胞内胆固醇的输出,从而促进巨噬细胞极化成促血管生成 M2 表型来调节 CNV,从而促进 nARMD 的进展。Wang 等[25]研究发现,磺基转移酶 2B1(sulfotransferase 2B1, SULT2B1)是胆固醇磺基化的关键酶,在胆固醇代谢中起重要作用,SULT2B1 的缺失激活了肝脏 X 受体(LXR),随后增加了 M2 巨噬细胞中 ATP 结合盒亚家族 G 成员 1(ATP-binding cassette transporter G1, ABCG1)和 ABCA1(ABCG1/A1)介导的胆固醇输出,进而阻止 M2 巨噬细胞极化,从而显著减少渗漏面积,抑制病理性血管生成。胆固醇代谢通过调节巨噬细胞活化促进 nARMD 进展的具体机制有待深入研究。

2.4 脂质代谢基因变异促进 nARMD 的进展 研究发现编码脂质代谢成分的基因发生遗传变异会导致视网膜和 Bruch 膜中脂质颗粒沉积和蛋白形成,从而影响视网膜功能[26]。编码脂质相关通路的基因与 nARMD 相关,包括载脂蛋白 E(apolipoprotein E, ApoE)、ABCA1、肝脂肪酶(hepatic lipase gene, LIPC)和胆固醇酯转移蛋白(cholesteryl ester transfer protein, CETP)[27]。ApoE 主要以三个等位基因变体(ε4、ε3 和 ε2)存在[28]。研究表明 ApoE 多态性与 nARMD 显著相关,ApoEε4 等位基因与 nARMD 风险降低相关,ApoEε2 等位基因与 nARMD 风险轻度增加相关[29-30]。但是 Fernández-Vega 等[31]发现 ApoEε2 等位基因在西班牙北部人群中对 nARMD 具有保护作用。与高密度脂蛋白(high-density lipoprotein, HDL)

代谢有关的基因变异包括肝脂肪酶(hepatic lipase gene, LIPC)、胆固醇酯转移蛋白(cholesteryl ester transfer protein,CETP)和 ABCA1[32-34]。ABCA1 在细胞中负责胆固醇输出[35]。RPE 特异性消融 ABCA1 引起小鼠 RPE 内脂质积累、RPE 和光感受器变性以及视力丧失,nARMD 相关的 ABCA1 基因变异会降低其在 RPE 细胞中的表达[36]。在不同种族、国家中,ApoEε2 等位基因与 nARMD 的关系还有待于进一步研究。

3 脂质代谢紊乱介导 nARMD 进展的机制

3.1 脂质代谢紊乱刺激氧化应激促进 nARMD 进展

nARMD 的主要病理变化是在氧化应激下视网膜外层低密度脂蛋白容易转化为氧化低密度脂蛋白(oxidized low-density lipoprotein, OxLDL),从而促进 CNV 的发展[37-38]。在维持视网膜氧供应和消耗之间的稳态中,视网膜局部氧代谢环境起着至关重要的作用,视网膜不断地将光转化为视觉,需要大量的能量,并产生活性氧(reactive oxygen species, ROS),如超氧化物、羟基自由基、过氧化氢和单线态氧为正常的代谢产物[39]。ROS 是生理条件下由氧化代谢产生,其参与正常细胞代谢,ROS 积累会损伤光感受器细胞、线粒体、溶酶体等结构,产生 ROS 的主要结构是线粒体,线粒体损伤时,ROS 产生随之增加,造成恶性循环[40]。氧化应激是指由于细胞产生有效抗氧化反应的能力无法应对过量的 ROS 或氧化剂而导致的不平衡[41]。脂质代谢失调时,在黄斑富含 ROS 的环境中,RPE 和玻璃膜疣中脂肪的过量积累可能会引发脂质氧化[42]。脂质积累提高了 ROS 的产生,游离脂肪酸水平升高持续刺激氧化应激[43]。氧化应激可以导致脂质过氧化,脂质过氧化激活氧化敏感转录因子如 NF-κB,刺激一系列炎症细胞因子的表达,从而导致炎症反应及 nARMD 的进展[44]。脂质过氧化可能和氧化应激相互作用来促进 nARMD 进展。丙二醛(malondialdehyde, MDA)是脂质过氧化的主要副产物,Ye 等[45]发现小鼠体内注射 MDA 可以增加激光诱导的 CNV 体积。以上研究表明了 MDA 和 nARMD 的关系,其中具体机制的进一步阐明对 nARMD 机制的研究具有重要的意义。

3.2 脂质代谢紊乱抑制自噬促进 nARMD 进展 自噬是一种溶酶体介导的分解代谢过程,用于维持细胞和有机体稳态,其已与多种疾病有联系[46]。细胞自噬功能减退及自噬通量下降是促进 nARMD 发展的关键因素之一[47]。nARMD 的特征是细胞增殖和 CNV,RPE 在 nARMD 发病机制中起关键作用。RPE 细胞在维持光感受器的稳态发挥重要的作用,表现在吞噬、降解和回收在视觉循环中脱落的光感受器外段(photoreceptor outer segment, POS)[48]。在正常的视觉周期中,RPE 细胞不断暴露在光线下并吞噬富含脂质的 POS[49]。RPE 自噬可以保护细胞免受氧化应激损伤,在早期 ARMD 中,急性氧化应激增加了 RPE 自噬,然而在 ARMD 的晚期,氧化应激负荷过高时自噬损伤,自噬的损伤可能会加剧氧化应激,导致无法清除受损细胞器[50]。脂质代谢紊乱可能通过介导自噬和氧化应激相互作用来促进 nARMD 的进展。Heckel 等[51]研究表明血脂异常和自噬均与 nARMD 发病机制有关,游离脂肪酸受体 1(free fatty acid receptor 1,FFAR1)可以感知甘油三酯衍生的脂肪酸,进而抑制调节自噬的转录因子 EB(transcription factor EB, TFEB),从而限制了光感受器的自噬,因此过量循环脂质引发了自噬的下降,加剧了光受体的能量衰竭,刺激血管通透因子(vascular endothelial growth factor A, VEGFA)的产生,从而驱动代偿性血管生成,导致 nARMD。哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)通路是细胞代谢和生长的重要调节因子,也是调节自噬的关键分子[52]。mTOR 是一种蛋白激酶,通过磷酸化下游靶蛋白来调节代谢、增殖、分化和自噬等生物过程,在 RPE 细胞中,mTOR 通路参与自噬的负调控[53]。雷帕霉素可抑制雷帕霉素靶蛋白 C1(mammalian target of rapamycin C1, mTORC1)并激活自噬,通过阻断 RPE 细胞在氧化应激下的有害变性来保持光感受器功能[54]。雷帕霉素会增强抗 VEGF 功能,减少内皮细胞增殖并抑制 CNV[55]。然后另一研究发现抑制 nARMD 的自噬可以增强抗 VEGF 功能[56]。鉴于自噬的激活和对抗 VEGF 功能在 nARMD 中具有相反的结果,需要进一步的研究来确定雷帕霉素在 nARMD 治疗中的机制。mTOR 自噬通路抑制剂已用于治疗多种疾病,然而目前尚不清楚它们是否可以有效且安全地用于治疗 nARMD, mTOR 在 nARMD 中作用机制的深入研究可为开发安全有效的治疗方案提供重要依据。

4 脂质代谢相关因子成为 nARMD 治疗潜在靶点

4.1 脂联素为 nARMD 治疗潜在靶点 脂联素(adiponectin, APN)是一种脂肪因子,在调节能量稳态、碳水化合物和脂质代谢以及免疫调节方面起着核心作用[57]。APN 可降低 VEGF 水平并抑制 CNV[58]。Osada 等[59]通过使用脂联素受体 1(adiponectin receptor 1, AdipoR1)敲除小鼠相关基因,证明了 AdipoR1 缺失对视网膜异常脂质代谢以及视网膜神经变性的影响,此外,他们利用原位杂交技术发现 AdipoR1 mRNA 在小鼠视网膜的光感受器内段(photoreceptor inner segment, PIS)强烈表达,出生后发育期间在 POS 表达增加,视网膜 AdipoR1 的表达对超长链脂肪酸延长酶 2(verylong chain fatty acidelongase, ELOVL2)的诱导至关重要,ELOVL2 诱导可以提供足够的 DHA, DHA 对 POS 形成至关重要,因此 ELOVL2 诱导可能是维持适当的感光细胞功能和存活的必要步骤。一项研究表明,APN 可以部分介导 ω3-LC-PUFA 对 nARMD 小鼠模型中的 CNV 抑制作用,调节 APN 通路与富含 ω3-LCPUFA 的饮食相结合可能会增强 ω3-LCPUFA 对 nARMD 患者保护作用[60]。目前需要更多的研究来进一步调查和阐明 APN 在 nARMD 中的作用以及潜在的分子机制,以更好地了解这一途径的具体作用机制。

4.2 LXR 为 nARMD 治疗潜在靶点 肝脏 X 受体(liver X-activated receptor, LXR)是一种配体激活的核转录因子[61],可调节与 CNV 相关的各种过程,包括脂质代谢[62-63]和胆固醇转运[64-66]。脂质蓄积和炎症是 nARMD 发病机制的关键因素[67-68]。Wu 等[69]通过使用激光光凝诱导 CNV 的小鼠,发现 LXR 激动剂通过 NF-κB 激活途径中 NF-κB p65 的核移位和增强 ATP 结合盒转运子 G1(ABCG1)依赖的脂质运输来减少炎症反应。Peters 等[70]

研究发现,胆固醇输出在 RPE 中的具有稳态作用,LXR 激动剂通过刺激 ABCA1 表达增加细胞胆固醇输出可能减轻脂质负荷,提高 RPE 存活率并降低发生 nARMD 的风险。因此,LXR 激动剂是一种很有前途治疗 nARMD 的候选药物。

4.3 过氧化物酶体增殖物激活受体 α 为 nARMD 治疗潜在靶点 过氧化物酶体增殖物激活受体 α(peroxisome proliferator-activated receptor alpha,PPARα)是肝脂质代谢的关键调节因子[71]。PPARα 与类视黄醇 X 受体(retinoid X receptors, RXRs)结合并进入细胞核,这些受体可以结合到 DNA 作为异二聚体和转录因子的功能,激活 PPAR 介导的基因表达[72]。Zhao 等[73]研究发现,将非诺贝特(PPARα 激动剂)注射到大鼠玻璃体中可以抑制 CNV,其中 VEGF-C 和 VEGFR-3 参与了 CNV。由于药物向视网膜递送效率低下,非诺贝特通过全身给药的作用未达到预期效果,利用负载非诺贝特的可生物降解纳米颗粒注射到玻璃体内,可实现高载药量和延长药物释放时间,从而对 nARMD 治疗具有长期有效的作用[74]。Chen 等[75]发现视网膜下纤维化是 nARMD 一种常见的病理变化,可导致 nARMD 的视力丧失,非诺贝特通过抑制 TGF-β-Smad2/3 信号传导和 Wnt 信号传导以及降低下游结缔组织生长因子(connective tissue growth factor, CTGF)表达来抑制视网膜下纤维化。综上所述,PPARα 激动剂在 nARMD 的实验模型中显示出良好的治疗效果,下一步的临床研究可以更好的揭示 PPARα 在 nARMD 发生发展中的重要作用。

5 小结

目前 nARMD 治疗局限于抗 VEGF 药物,但是抗 VEGF 药物在临床应用过程中存在诸多弊端,亟需治疗 nARMD 的新型药物及策略。本文主要阐述了脂质代谢在 nARMD 进展中的重要作用,包括膳食补充 ω-3 LCPUFA、胆固醇代谢和脂质代谢基因变异对 nARMD 进展的影响。脂质代谢紊乱促进 nARMD 进展的机制主要涉及刺激氧化应激、抑制自噬及二者间的相互作用。在研究中,ApoEε2 等位基因与 nARMD 风险呈相反的结果,而膳食补充 ω-3 LCPUFA 与 nARMD 进展到晚期的结果也呈相反的趋势,因此强调了不同种族及不同国家展开联合研究的重要性。雷帕霉素激活自噬虽然能增强抗 VEGF 功能,但与抑制 nARMD 的自噬增强抗 VEGF 功能的观点存在矛盾,提示雷帕霉素在抗 VEGF 功能可能涉及多个机制,其具体机制还需要进一步深入研究。一些潜在的新型药物,如 APN 激活剂、LXR 激动剂、及负载 PPARα 激动剂的可生物降解纳米颗粒,在动物实验中展现出积极的治疗效果,尽管在动物实验中获得了积极结果,但要全面评估调节脂质代谢在 nARMD 中的可行性和有效性,仍需要展开临床研究。未来的研究方向包括深入探讨脂质代谢与 nARMD 之间的精细调控机制,寻找新的脂质相关标志物和治疗靶点,为 nARMD 的早期诊断和个体化治疗提供更多的手段。基于对脂质代谢的深刻理解,设计更具针对性的药物和治疗策略,有望提高治疗效果并降低副作用。

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