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·综述·

载脂蛋白A1及其模拟肽在眼科疾病中的研究新进展

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[摘 要] 近年来，脂质代谢紊乱与眼科疾病关系密切。体外研究和临床前模型显示，高密度脂蛋白(high density lipoprotein，HDL)及其主要蛋白成分载脂蛋白A1(apolipoprotein A1，apoA1)对内皮细胞具有抗氧化、抗炎和抗凋亡作用，对血管具有强大的保护作用。ApoA1模拟肽能够模拟apoA1功能，且分子质量更小，前景非常乐观。而动物实验及人体试验均证实了模拟肽D-4F口服使用的安全性及有效性，因此目前研究最为广泛。目前来说，对于apoA1及其模拟肽在眼科疾病的研究中属于萌芽阶段。本文总结了apoA1及其模拟肽的结构，及其在眼科疾病如视光学、角膜病、玻璃体视网膜疾病中的研究进展，为apoA1及其模拟肽在眼科的进一步研究及开发利用提供参考。

[关键词] 载脂蛋白A1；模拟肽4F；角膜；玻璃体视网膜疾病

Advances of apolipoprotein A1 and its mimetic peptide in ophthalmic diseases

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Abstract The recent researches indicate that the disorder of lipid metabolism is closely related to ophthalmic diseases. In vitro studies and preclinical studies have shown that high density lipoprotein (HDL) and its main structural protein apolipoprotein A1 (apoA1) have superior efficacy in blood vessel protection, with antioxidant, anti-inflammatory and antiapoptotic effects on endothelial cells. Prospect of the ApoA1 mimetic peptide is very optimistic as it can mimic the function of apoA1, and its molecular weight is smaller. The safety and efficacy of oral use of mimetic peptide D-4F have been confirmed in both animal experiments and clinic trials. Thus, it had been extensively studied. In this paper, we reviewed the structure of apoA1 and its mimetic peptide, as well as their

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researches related to ophthalmic diseases, such as optometry, corneal diseases and vitreoretinal diseases, so as to provide reference to further researches in apoA1 and its mimetic peptide in the of ophthalmic diseases.

Keywords apolipoprotein A1; mimetic peptide 4F; cornea; vitreoretinal disease

近来流行病学研究[1]发现：血浆高密度脂蛋白(high-density lipoprotein，HDL)水平升高可使心血管疾病的患病风险降低，它们之间存在负相关关系。其中，载脂蛋白A1(apolipoprotein A1，apoA1)约占HDL蛋白组成成分的70%，是HDL的主要蛋白质成分，构成了HDL承载磷脂和胆固醇的骨架[2-3]。它是一种多功能蛋白质，其作用有抗动脉粥样硬化[3-4]、参与胆固醇的逆向转运[5-7]，调节炎症和免疫反应[8-10]、抗氧化[11]、抑制肿瘤[3]等。ApoA1在心血管疾病中研究较多，而在眼科中的作用探讨甚少。近几年多项研究结果表明apoA1表达水平与眼科疾病相关，在眼科疾病的早期诊断、治疗及预后方面进行初步的探讨。因此，进一步研究apoA1及其模拟肽在眼科疾病中的作用机制可能为眼科疾病的诊疗带来新启示。

1 ApoA1 及其模拟物

ApoA1的一级结构由243个氨基酸组成，由10个两亲性的α卵形螺旋结构组成它的二级结构，分子质量约为28 kDa[12]。两亲性的性质使它的肽蛋白既能隔离脂质，又能在水环境中穿行。ApoA1是比脂质水平更稳定的蛋白片段，不受膳食状态的显著影响[13]。因此，研究apoA1比HDL更具有现实意义。Reddy等[4]合成了第1个apoA1模拟肽，是一种短螺旋肽，模拟肽由18个氨基酸组成，分子质量2.31 kDa，随后通过修饰，能够模拟apoA1的功能。基于疏水面上苯丙氨基酸(F)残基的数量，apoA1模拟肽分为2F，3F，4F，5F，6F及7F。动物实验证明4F及5F有很高的活性[14]，其中4F显示出物理化学特性最有利并且生物活性最高。4F具有抗炎作用，因为它以高亲和力结合氧化磷脂和脂肪酸氢过氧化物在细胞膜上，而且明显比apoA1本身更抗动脉粥样硬化。4F显著减少动物模型大动脉粥样硬化病变[4,15-16]。4F抑制ApoE null小鼠动脉粥样硬化，不改变血浆胆固醇，但清除血浆中氧化脂质，从而建立4Fs改善脂质介导炎症的作用[14]。4F有2种合成形式，全左旋-氨基酸(L-4F)合成及全右旋-氨基酸(D-4F)合成，目前也广泛地被应用于科研中[17]。体外研究[18-19]显示：L-4F和D-4F两种同分异构体有着类似特性，但L-4F蛋白质在胃肠道更易受蛋白酶水解，因此不能口服，而D-4F动物实验及人体试验均证实口服使用的安全性及有效性。D-4F具有18个氨基酸肽链片段，包含4个F残基，并由其合成D-氨基酸。D-4F具有抗动脉粥样硬化[20]、逆向转运胆固醇和抗炎等作用[21]，且临床试验已证实人体口服apoA1模拟肽D-4F安全有效，因此临床应用前景最大。其他正在被研究的apoA1模拟肽有apoA Kringle V和apoA1结合蛋白等。

2 ApoA1 在视光学疾病的研究进展

ApoA1被认为是有效的近视蛋白生物标志物，视网膜中apoA1的水平可以有效抑制近视的发展。近视是视力下降的最常见原因，由于眼轴伸长可能导致高度近视性疾病或诱发其他眼部并发症。

Bertrand等[22]通过蛋白质组学研究检测了透镜诱导性近视(lens-induced myopia，LIM)或透镜诱导性远视(lens-induced hyperopia，LIH)的雏鸡视网膜中表达差异的蛋白，发现LIH眼视网膜的apoA1表达水平呈升高趋势。氧化应激和脂质代谢是参与补偿性眼轴增长的途径。玻璃体腔注射过氧化物酶体增殖剂激活受体激动剂(PPAR-alpha agonist)可抑制眼部生长，从而增加视网膜apoA1的表达[23-24]。因此，apoA1被认为是近视眼发育的“停止”信号，它被认为是有效的近视蛋白生物标志物。雏鸡LIH视网膜及巩膜apoA1水平升高，提示视网膜中的apoA1可以有效抑制近视的发展，可能抑制转化生长因子(transforming growth factor，TGF)-beta 28的激活，对眼球生长起阻滞信号作用。视黄酸是一种已被证实的调节近视眼生长的信号，Summers等[25]发现雏鸡脉络膜和巩膜中的apoA1与视黄酸具有一种新的调节反馈机制，它以浓度依赖的方式控制出生后的眼球生长。Chun等[26]研究玻璃体apoA1的表达差异，进一步证实了apoA1与过度眼球生长有关。除apoA1外，目前被鉴定为眼生长差异的生物标志物还有卵转铁蛋白

(ovotransferrin)、羟基茜草素(purpurin)等[27]，它们都属于结合蛋白一类，确切作用尚不清楚。但apoA1与许多已知在调节眼睛生长中重要的神经递质的潜在相互作用。这一系列的研究表明近视与代谢有关，并伴有视网膜蛋白水平的能量生成改变和氧化应激，而apoA1作为一种有效的近视蛋白生物标志物以研究它在抑制近视进展中的作用。

3 ApoA1 在角膜疾病的研究进展

在眼前节中，apoA1存在于角膜基质细胞、角膜角质细胞和角膜内皮细胞[28]。若apoA1缺乏可致：丹吉尔病(Tangier disease，TD)、鱼眼病(fish eye disease，FED)和卵磷脂胆固醇酰基转移酶(lecithin-cholesterol acyltransferase，LCAT)缺乏症[29]。丹吉尔病和鱼眼病是由转运蛋白ATP结合盒运转体A1(ATP-binding cassette transporter A1，ABCA1)和LCAT突变引起的[30-31]。LCAT是肝分泌的一种酶，与血液中的HDL一起循环。这种酶对血浆胆固醇酯化起到催化作用，增加HDL携带胆固醇的能力，并可从组织中清除胆固醇。目前研究的主要机制为：apoA1缺乏，脂质清除机制出现缺陷，导致胆固醇在角膜基质内沉积，在临床上可表现为不同程度的角膜混浊[30-31]，可严重影响视力。在某些情况下，需要角膜移植才能恢复正常视力。角膜混浊，是由于角膜的脂质(包括胆固醇)的积累所致。这三种疾病与胆固醇从组织反向转运(reverse cholesterol transport，RCT)异常有关，并伴有缺陷和异常的HDL颗粒分布[28]。ApoA1等载脂蛋白与ABCA1相互作用产生盘状HDL，apoD可激活LCAT，但apoA1是LCAT最有效的激活剂，研究发现apoA1在角膜中不表达，但它聚集在角质细胞中。

4 ApoA1 及其模拟肽在玻璃体视网膜疾病中的研究进展

ApoA1在RCT中起重要作用。Tserentsoodol等[33-34]推测含有apoA1的HDL通过清除有害的氧化脂质促进了脂质在视网膜内的运输。发现视网膜色素上皮(retinal pigment epithelium，RPE)中apoA1 mRNA的水平高于神经上皮层，表明RPE是眼内apoA1的主要来源。D-4F可以清除细胞内活性氧，抑制脂质过氧化物的产生，提高内源性抗氧化活性。D-4F可以通过抑制氧化低密度脂蛋白(oxidized low-density lipoprotein，oxLDL)诱导的色素上皮衍生因子(pigment epithelium-derived factor，PEDF)下调来降低氧化应激和静脉内皮细胞(vein endothelial cells，VEC)损伤[33-35]。Biswas等[36]研究表明：线粒体胆固醇转运蛋白 (translocator protein，TSPO)在人和小鼠RPE细胞中高表达，显著增加了胆固醇从RPE细胞向apoE，apoA1和HDLs的外排。随着年龄的增长，RPE的TSPO表达降低，胆固醇外排受损，这可能增加了RPE分泌的Bruch膜脂蛋白(Bruch's membrane lipids，BrM-LPs)消除脂质的负担[37]。

Zhang等[38]通过糖尿病视网膜病变(diabetic retinopathy，DR)10年前瞻性队列研究推测apoA1水平升高可能是DR的保护因素之一。在DR患者中，血清apoA1水平呈负相关[39]。Sasongko等[40]用logistic回归模型分析DR的新型风险标志物，血清apoA1水平下降和视网膜小动脉弯曲程度可能是DR的新的独立危险标记。在临床研究中，在糖尿病患者中玻璃体apoA1的水平上调[41]，这表明apoA1是一个强有力的活性氧清除器，可能保护糖尿病患者的视网膜免受氧化应激[42]。Ding等[43]推测由于apoA1是氧化反应物的有效清除剂，故DR的环境可以刺激apoA1表达。Simó等[44]还假设视网膜apoA1产生增加是一种对抗DR的保护性代偿机制，因此，视网膜apoA1产生较少的DR患者更有可能出现视网膜脂质沉积和高硬渗出物形成。Tan等[45]发现：apoA1能抑制高糖环境下人视网膜血管内皮细胞(retinal vascular endothelial cells，RVECs)中血管内皮生长因子(vascular endothelial growth factor，VEGF)的表达，由此对人视网膜血管内皮细胞(human retinal vascular endothelial cells，HRECs)的增生、迁移和成管能力起到抑制作用，对高糖环境中的RVECs提供保护作用，为DR的诊断治疗及预防提供新的思路。

一项Meta分析[46]指出：晚期年龄相关性黄斑变性(age-related macular degeneration，AMD)与氧化、脂质沉积、补体激活和巨噬细胞募集的途径有关。全基因组相关性研究表明，AMD的病理生理是基于脂质代谢失调、氧化应激和慢性炎症[47]。含胆固醇的软玻璃膜疣和视网膜下结节样沉积物(subretinal drusenoid deposits，SDDs)分别发生于RPE基底外侧和根尖侧，是晚期AMD的独立危险因素[48]。通过透射电镜，发现软玻璃膜疣

富含脂质[49-50]，包括载脂蛋白B，E和A1的大脂蛋白颗粒[51]。Fang等[52-54]推断apoA1结合蛋白(apoA1 binding protein，AIBP)增强了内皮细胞和巨噬细胞的胆固醇外排，在内皮细胞中，AIBP与含apoA1的HDL结合，加速胆固醇外流，从而降低脂质筏的含量，抑制脂质筏锚定的血管内皮细胞生长因子受体2(vascular endothelial growth factor receptor 2，VEGFR2)信号转导，从而限制血管生成[55]。Mao等[56]则推断AIBP以一种分泌酶依赖的方式下调Notch，以此抑制小鼠的病理视网膜新生血管生成，从而调节血管生成。

5 ApoA1的模拟肽在眼科疾病中的治疗

ApoA1模拟肽在眼科疾病的中的治疗研究主要集中在眼部抗血管生成疾病上。最初，研究者主要关注apoA Kringle V(Kringle 5-like domain)。KV11是一种来源于人apoA KV的小型聚体肽。Zhao等[57]发现它在体外可有效抑制视网膜内皮细胞迁移，在体内可降低视网膜病理新生血管形成，且同时具有足够的视网膜穿透能力和良好的安全性。AU6，同为来源于apoA Kringle V的新型六氨基酸肽，也能有效抑制致病性脉络膜新生血管(choroidal neovascularization，CNV)[58]。KV11和AU6成为眼部抗血管生成治疗的潜在候选药物。随后，Rudolf等[59]先发现apoA1模拟肽4F是一种治疗重要的AMD疾病过程的新方法，从药理学角度发现4F可减少酯化胆固醇(esterified cholesterol，EC)和恢复Bruch膜的超显微结构。然后在老年非灵长类动物模型中[60]，通过玻璃体腔注射L-4F，可清除Bruch膜中性脂质、酯化胆固醇和膜攻击复合物。ApoA1模拟肽4F为治疗AMD的潜在病因提供了一个新方法。近来，Zhu等[55]发现：apoA1结合蛋白(binding protein，AIBP)联合抗VEGF治疗，可有效克服抗VEGF耐药并有效抑制CNV，因此该联合方案是一种有前景的对抗CNV抗VEGF耐药性的治疗方案。

6 结语

ApoA1在脂质代谢与眼科疾病的研究中扮演着重要的角色，apoA1可以有效抑制近视的发展，控制眼轴伸长；可加速胆固醇逆向运转，防治胆固醇在角膜基质内沉积，减少角膜混浊；加快视网膜脂质逆向运转，降低氧化应激和内皮细胞损伤，抑制视网膜新生血管生成；减少脂质堆积，恢复Bruch膜显微结构。而apoA1模拟肽可模拟apoA1的作用，其中D-4F具有分子质量小、易合成、口服安全有效的优势，更适合临床应用及推广。ApoA1模拟肽率先在眼部抗血管生成疾病的研究中小有成效，但目前apoA1及其模拟肽作用的具体机制尚未完全清楚，将来需要更多的研究深入探讨，为眼科疾病的治疗提供新思路。

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