

doi: 10.3978/j.issn.1000-4432.2020.12.01

View this article at: <http://dx.doi.org/10.3978/j.issn.1000-4432.2020.12.01>

· 综述 ·

## 载脂蛋白A1及其模拟肽的功能及与视网膜疾病关系的研究进展

陈珠婷 综述 胡洁, 胡安娣娜 审校

(中山大学中山眼科中心, 眼科国家重点实验室, 广州 510060)

**[摘要]** 视网膜疾病的发病机制错综复杂, 涉及氧化应激、病理性血管生成以及脂质沉积等。载脂蛋白A1(apolipoprotein A1, apoA1)及其模拟肽具有抗炎、抗氧化、逆向转运脂质及调节血管生成等功能。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。近年研究发现, apoA1及其模拟肽与糖尿病视网膜病变、年龄相关性黄斑变性等多种视网膜疾病密切相关, 本文从apoA1及其模拟肽的分子结构、产生与分布、主要生理功能、及其在视网膜疾病研究中的最新进展进行了综述。

**[关键词]** 载脂蛋白A1; 模拟肽; 视网膜疾病; 脂质逆转运; 抗炎

## Research progress on function of apolipoprotein A1 and its mimetic peptides and the relationship with retinal diseases

CHEN Zhuting, HU Jie, HU Andina

(State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou 510060, China)

**Abstract** The pathogenesis of retinal diseases is complex, involving with oxidative stress, pathological angiogenesis and lipid deposition. Apolipoprotein A1 (apoA1) and its mimetic peptides have anti-inflammatory, antioxidant, reverse lipid transport and angiogenesis regulation functions. The safety and effectiveness of oral use of mimetic peptide D-4F have been confirmed in both animal and human studies. Therefore, D-4F is the most widely studied at present. In recent years, apoA1 and its mimetic peptides are closely related with diabetic retinopathy, age-related macular degeneration and other retinal diseases. In this article, the molecular structure, production and distribution, main physiological functions of apoA1 and its mimetic peptides, as well as the latest progress on the relationship with retinal diseases were reviewed.

**Keywords** apolipoprotein A1; mimetic peptide; retinal disease; reverse lipid transport; anti-inflammatory

收稿日期 (Date of reception): 2020-09-12

通信作者 (Corresponding author): 胡安娣娜, Email: huandina@163.com

基金项目 (Foundation item): 国家自然科学基金 (81500735; 81970807); 广东省自然科学基金 (2017A030313494)。This work was supported by the National Natural Science Foundation (81500735; 81970807) and Natural Science Foundation of Guangdong Province (2017A030313494), China.

载脂蛋白A1(apolipoprotein A1, apoA1)是高密度脂蛋白(high-density lipoprotein, HDL)的主要结构及功能蛋白<sup>[1]</sup>。ApoA1及其模拟肽具有抗炎、抗氧化、逆向转运脂质、调节血管生成等作用<sup>[2-5]</sup>。有研究<sup>[6]</sup>证实apoA1模拟肽能够抑制肿瘤新生血管、apoA1在视网膜各层均有分布,并且apoA1能逆向转运视网膜内脂质,减少视网膜内脂质沉积<sup>[7]</sup>,减缓年龄相关性黄斑变性(age-related macular degeneration, AMD)的进展。这提示apoA1或能成为治疗视网膜疾病的一种新的策略。本文从apoA1及其模拟肽的分子结构、产生与分布、主要生理功能及其在视网膜疾病研究中的最新进展进行了综述,旨在为视网膜疾病的治疗提供新的思路。

## 1 ApoA1 及其模拟肽的分子结构

ApoA1是HDL的主要结构及功能蛋白,由243个氨基酸组成,其二级结构中包括10个特征性的两亲性 $\alpha$ 螺旋结构,在apoA1与脂质的相互作用中发挥重要功能<sup>[8]</sup>。研究<sup>[2-4,9]</sup>表明apoA1具有抗炎、抗氧化、逆向转运脂质及调节血管生成等作用,具有良好的临床应用前景。但其相对分子量大、必须静脉给药,使其在临床上的应用受到了限制。

ApoA1模拟肽是一类通过构建两亲性 $\alpha$ 螺旋结构以模拟apoA1的脂质转运功能的多肽,此外还具有分子量小、易合成的优势,更适合临床应用及推广<sup>[10]</sup>。基于疏水面上苯丙氨酸(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,其中4F的生物活性最高并且理化特性最有利。4F可以全部由左旋-氨基酸(L-4F)或右旋-氨基酸(D-4F)合成,目前研究也最为广泛<sup>[11]</sup>。体外研究<sup>[12]</sup>显示L-4F和D-4F两种同分异构体有着类似特性,但由于L-4F在胃肠道更易被蛋白酶水解,因此不能口服,而肠道是D-4F的主要吸收部位,动物实验及人体试验均证实了D-4F口服使用的安全性及有效性。D-4F是一种由18个D-氨基酸组成的肽,包含4个F残基,其三级结构类似于apoA-1,但没有序列同源性。D-4F也具有与apoA1类似的抗炎、抗氧化、逆向转运脂质及调节血管生成等作用<sup>[13-16]</sup>。

## 2 合成及分布

ApoA1主要在肝和小肠合成,近年的研究<sup>[17]</sup>

发现, apoA1在视网膜各层均有分布,并且在视网膜色素上皮(retinal pigment epithelium, RPE)层最为丰富。循环中的HDL和低密度脂蛋白(low density lipoprotein, LDL)通过RPE上的B类清道夫受体(class B scavenger receptors, SR-B)和低密度脂蛋白受体(LDL-receptor, LDLR)进入视网膜,随后传递到视网膜其他区域。腺苷三磷酸结合盒转运体(ATP-binding cassette transporter A1, ABCA1)、SR-BI、SR-BII和CD36是参与apoA1介导的视网膜内脂质逆转运的关键蛋白<sup>[18-19]</sup>。在猴的视网膜中, ABCA1和apoA1定位于神经节细胞层(ganglion cell layer, GCL)、RPE和视状光感受器内段, SR-BI和SR-BII主要定位于GCL和光感受器外段<sup>[20]</sup>。ABCA1和apoA1在猴视网膜中的定位表明视网膜内存在独立的脂质转运途径。

## 3 ApoA1 及其模拟肽的功能

### 3.1 脂质转运

HDL及apoA1可通过胆固醇逆转运,将胆固醇从周围组织转运至肝进行再循环或以胆酸的形式排泄,减少胆固醇的聚积,从而发挥血管保护作用。这种血管保护作用主要是通过胆固醇逆转运来实现的。胆固醇外流是胆固醇逆转运的第一步, ABCA1在胆固醇外流方面发挥关键作用<sup>[21]</sup>。循环系统中的HDL和LDL可通过RPE上的SR-Bs和LDLR进入视网膜<sup>[20]</sup>。RPE分解LDL,利用apoA1和载脂蛋白E(apolipoprotein E, apoE)重组高密度脂蛋白样颗粒,通过ABCA1转运体分泌到光感受器间质(interphotoreceptor matrix, IPM)。在IPM中,高密度脂蛋白颗粒在胆固醇酰基转移酶及胆固醇酯转移蛋白的帮助下摄取更多的脂质,因此,利用高密度脂蛋白颗粒作为中间物, SR-Bs和CD36作为受体,脂质在RPE和光感受器之间来回转运。SR-Bs和CD36有助于筛选氧化脂质含量高的脂质颗粒。Müller细胞也可能在传递和接受RPE和光感受器的脂蛋白颗粒方面发挥作用。随后, RPE还可通过分泌低密度脂蛋白和高密度脂蛋白样颗粒回到循环以维持体内平衡<sup>[20]</sup>。ApoA1作为视网膜内脂质逆向转运的关键因素,能够阻止脂质在视网膜中的积聚。

### 3.2 抗氧化

氧化应激和脂质过氧化会促进糖尿病的发

展。视网膜是唯一能直接和频繁地暴露在光线下的神经组织, 而许多脂质, 特别是多不饱和脂肪酸(主要位于感光细胞外段)和胆固醇酯极易受到光氧化的影响, 被氧化的脂质对视网膜细胞具有极强的毒性<sup>[22]</sup>。研究<sup>[23]</sup>表明: apoA1除了逆向转运视网膜内的脂质, 预防脂质毒性外, 还是一种有效的活性氧清除剂。4F肽的治疗能够显著减少糖尿病小鼠模型肝中的氧化脂肪酸<sup>[24]</sup>。HDL的抗氧化性与血清对氧磷酶1(paraoxonase 1, PON1)的功能密切相关。PON1具有防止脂质氧化的能力, 甚至在炎症压力过大的情况下会使氧化脂质失活<sup>[25]</sup>, HDL保护自身和其他含脂分子和结构的能力会降低, 而apoA1模拟肽4F能够改善各种动物模型中的HDL功能, 这与apoA1模拟肽4F积极结合氧化脂质的能力有关<sup>[26]</sup>。因此, apoA1模拟肽4F可能在保护视网膜免受糖尿病引起的氧化应激中起重要作用。

### 3.3 抗炎

4F能与氧化磷脂和脂肪酸氢过氧化物高亲和力地结合, 具有抗炎作用<sup>[7]</sup>。ApoA1可减少脂多糖(lipopolysaccharide, LPS)诱发的炎症反应。Dai等<sup>[27]</sup>报道apoA1模拟肽4F可防止LPS引起的血压和血管反应性的变化。这可能与4F促进LPS在HDL的定位而导致的内毒素中和以及抑制LPS诱导的一氧化氮合酶2(nitric oxide synthase 2, NOS2)相关的血流动力学变化有关。此外, apoA1和apoA1模拟肽4F在炎症状态下能够通过抑制单核细胞趋化/黏附, 降低血管巨噬细胞含量发挥抗炎作用, Smythies等<sup>[28]</sup>报道, 4F能够通过调节单核细胞源性巨噬细胞(monocyte-derived macrophages, MDMs)上关键细胞表面受体的表达来调节MDMs的功能, 可能与促使其向抗炎表型分化有关。

### 3.4 调节血管生成

血管生成是指在原有血管的基础上形成新的血管的过程。包括血管基底膜的降解、内皮细胞迁移增殖、血管芽生、管腔形成、血管系统的成熟与重塑五个阶段。内皮细胞在血管生成中起主导作用。在正常生理条件下, 机体内促血管生成因子与抗血管生成因子之间的精确平衡调控着血管生成, 最终发育为成熟的血管。而在病理条件下, 缺氧、炎症等因素打破这种平衡, 导致不成熟的病理性新生血管生成<sup>[29]</sup>。

#### 3.4.1 促进生理性血管生成

生理性缺血介导的血管生成是在损伤或血管闭塞后血液供应受到限制, 组织供氧与需求之间出现慢性失衡, 随后的缺氧诱导缺血组织新生血管形成。研究<sup>[9]</sup>发现: apoA1能够促进生理性血管生成。在小鼠中, 利用腺病毒过度表达apoA1和输注apoA1均可诱导循环系统中内皮祖细胞(endothelial progenitor cells, EPCs)数量的增加<sup>[30]</sup>。体外研究<sup>[31]</sup>表明, HDL刺激内皮细胞的迁移。动物实验<sup>[32]</sup>表明: 静脉注射apoA1可促进小鼠后肢缺血模型中的新生血管形成并增加腓肠肌毛细血管密度。最近的研究<sup>[33]</sup>通过后肢缺血模型确定了SR-BI在调节体内血管生成中的作用。与野生型小鼠对比, 在SR-BI基因敲除鼠中, 输注rHDL后诱导新生血管的作用减弱。体外成管试验<sup>[34]</sup>也显示慢病毒介导的SR-BI shRNA敲除抑制缺氧环境下rHDL诱导的小管形成。此外, SR-BI基因敲除, 可减弱apoA1诱导的循环系统内EPCs的增加<sup>[35]</sup>。上述结果都支持apoA1通过血清道夫受体促进生理性血管生成的观点。

#### 3.4.2 抑制炎症性血管生成

与缺血诱导的新生血管形成不同, 病理性血管生成主要由炎症参与诱导, 包括两个主要途径: 1)炎症细胞因子/趋化因子对内皮细胞增殖和迁移的直接影响; 2)间接作用, 包括巨噬细胞最初向炎症部位募集, 而分泌大量促血管生成因子, 包括血管内皮生长因子(vascular endothelial growth factor, VEGF)、碱性成纤维细胞生长因子(basic fibroblast growth factor, bFGF)、肿瘤坏死因子 $\alpha$ (tumor necrosis factor  $\alpha$ , TNF- $\alpha$ )和粒细胞-巨噬细胞集落刺激因子(granulocyte macrophage-colony stimulating factor, GM-CSF)等<sup>[36]</sup>。研究<sup>[37]</sup>表明: 在兔慢性血管炎症模型中, apoA1模拟肽(ETC-642)可降低血管细胞黏附分子-1和细胞间黏附分子。在小鼠股袖动脉周围炎性血管生成模型中, apoA1抑制新生血管形成<sup>[38]</sup>。ApoA1及其模拟肽能抑制炎症诱导的血管生成。

### 3.5 抑制肿瘤生成

炎症和氧化应激在肿瘤的发生和发展中起着重要作用。apoA1及其模拟肽的抗肿瘤特性也已在多种类型的肿瘤中得到了验证, 包括黑色素瘤、结肠直肠癌和卵巢癌等<sup>[39-41]</sup>。D-4F治疗显著增加了遗传性乳腺癌小鼠模型的肿瘤潜伏期并抑制



了肿瘤的发展<sup>[42]</sup>。过表达apoA1的转基因动物模型在接种黑色素瘤和肺癌细胞时显示肿瘤发展的下降, 而敲除apoA1则有相反的效果<sup>[39]</sup>。皮下注射人apoA1还可以防止肿瘤转移生长, 提高接种过黑色素瘤细胞的小鼠的存活率<sup>[39]</sup>。ApoA1的过表达可以降低肿瘤体积, 提高了转基因卵巢癌小鼠模型的存活率<sup>[41]</sup>。促炎性溶血磷脂, 溶血磷脂酸(lysophosphatidic acid, LPA)能够增加血管生成, 促进肿瘤转移<sup>[43]</sup>。Su等<sup>[41]</sup>的体外实验表明, 4F肽能够显著抑制LPA诱导的卵巢癌细胞生长, 并显著降低卵巢癌小鼠模型中血浆中的LPA水平。LPA结合和清除可能是apoA1模拟肽抑制肿瘤发生的机制之一。Gao等<sup>[44]</sup>报道, apoA1模拟肽L-5F可减少体内肿瘤血管生成, 并抑制VEGF/bFGF刺激的增殖、迁移和侵袭, 以及人脐血管内皮细胞的管腔形成, L-5F还抑制VEGF和bFGF诱导的相应受体VEGFR2和FGFR1的激活, 以及下游信号通路。基于这些证据, apoA1模拟肽不仅可以去除LPA样的生物活性脂质, 还可以改变细胞膜的脂质组成/结构, 从而导致膜受体(如VEGFR2和FGFR1)功能的改变, 进而抑制炎症性血管生成。

## 4 ApoA1 及其模拟肽在视网膜疾病中的研究现状

### 4.1 ApoA1 及其模拟肽与糖尿病视网膜病变

视网膜新生血管(retinal neovascularization, RNV)是包含增殖性糖尿病视网膜病变在内的多种致盲性眼病的共同病理过程<sup>[45]</sup>。临床上抗VEGF药物的应用极大地改善了患者的视力, 但仍有30%~50%的糖尿病视网膜病变(diabetic retinopathy, DR)患者对抗VEGF治疗无反应或者反应低下<sup>[46]</sup>。此外, 抗VEGF治疗需要多次反复给药和频繁的随访等, 给患者带来极大的经济负担。因此, 有必要探索治疗RNV更安全、成本更低的治疗策略。D-4F能够减少糖尿病大鼠模型中内皮细胞脱落, 改善血管反应性<sup>[47]</sup>, 减少糖尿病性中风大鼠模型的血脑屏障渗漏, 增加紧密连接蛋白的表达, 抑制炎症<sup>[48]</sup>。但D-4F对视网膜屏障的作用尚未有研究报道。此外, apoA1模拟肽L-5F抑制VEGF及bFGF刺激的增殖、迁移和侵袭以及人脐血管内皮细胞的管腔形成, 还抑制VEGF和bFGF诱导的相应受体VEGFR2和FGFR1以及下游信号通路的激活<sup>[6]</sup>。ApoA1抑制高糖诱导的人视网膜血管内皮

细胞的增殖、迁移、成管以及VEGF的表达<sup>[49]</sup>。有部分学者<sup>[50]</sup>发现血清apoA1水平与DR的严重程度负相关。但Simo等<sup>[51]</sup>在DR患者玻璃体中, 以及糖尿病供体的视网膜中检测到了较高水平的apoA1, 基于apoA1在视网膜中抗炎、抗氧化、逆向转运脂质的保护作用, 推测视网膜apoA1的增高可能是对DR的一种保护性代偿机制。近期前瞻性研究<sup>[52]</sup>表明血脂与临床显著性黄斑水肿和硬性渗出物风险增加有关, 但与DR的进展或增殖性DR的发展无关。他汀类药物不能阻止DR的发展<sup>[53]</sup>。因此, 对于DR患者, 调节视网膜内脂质转运的机制可能比调节血清中的apoA1水平更为重要。也有学者<sup>[54]</sup>认为, apoA1的过度表达可能是DR的早期事件, 视网膜产生apoA1的能力较低的糖尿病患者更容易在视网膜发生脂质沉积(硬性渗出物), 从而引发DR。

### 4.2 ApoA1 及其模拟肽与 AMD

AMD是发达国家老年人致盲的一个常见原因, 脂蛋白沉积在AMD的发病机制中至关重要。多方面的证据表明, 软性drusen是AMD进展的最大眼内危险因素<sup>[55]</sup>。软性drusen是视网膜色素上皮基底层和Bruch膜之间细胞外物质的局灶性沉积<sup>[56-57]</sup>。软性druse的主要成分被认为是部分保存的RPE来源的大脂蛋白颗粒<sup>[58]</sup>。ApoA1作为视网膜内脂质逆向转运最关键的因素, 能够阻止脂质在视网膜中的积聚<sup>[7]</sup>。Rudolf等<sup>[59]</sup>在小鼠模型中通过玻璃体内注射apoA1的模拟肽L-4F, 证明了L-4F能够促进Bruch膜超微结构的恢复以及高效降低Bruch膜脂的药理学作用。同样地, 通过玻璃体腔注射L-4F, 老年非人类灵长类动物的Bruch膜脂大幅减少, 超微结构恢复, 这些证据表明, L-4F是治疗AMD的一个有潜力的候选药物。

### 4.3 ApoA1 及其模拟肽与其它眼部疾病

ApoA1能够抑制透镜诱发的雏鸡近视的发展<sup>[60-61]</sup>。以apoA1蛋白为原料制备的HDL突变体作为一种具有治疗活性的药物载体有助于脉络膜新生血管(choroidal neovascularization, CNV)的治疗。研究<sup>[62]</sup>表明: 在激光诱导的CNV小鼠模型中, 注射携带抗血管生成药物帕唑帕尼的最佳突变体1周后, CNV病灶显著减小。孔源性网脱患者视网膜下液中apoA1的存在表明, 只有低分子血浆蛋白更容易从脉络膜毛细血管-色素上皮复合体逃脱<sup>[63]</sup>。此外, 孔源性视网膜脱离合并脉络膜脱离患者的玻

璃体液中的apoA1水平较单纯孔源性视网膜脱离以及特发性黄斑前膜患者显著增高,提示apoA1有望成为孔源性视网膜脱离合并脉络膜脱离的一个特异性生物标志物<sup>[64]</sup>。

## 5 结语

综上所述, apoA1及其模拟肽具有抗炎、抗氧化、逆向转运视网膜内脂质及调节血管生成等作用,是治疗多种致盲性眼病的一个有潜力的药物。ApoA1模拟肽D-4F具有分子量小、易合成、口服安全有效的优势,更适合临床应用及推广。目前关于apoA1及其模拟肽在视网膜疾病中的研究相对较少,基于其抵抗炎症性新生血管的功能,还可推测apoA1及其模拟肽不仅对治疗DR有效,还有望治疗其他新生血管性疾病,例如角膜新生血管、视网膜静脉阻塞、新生血管性青光眼等,同时也将更加全面地深入研究apoA1及其模拟肽的生物学功能及其作用机制。

## 参考文献

- Delk SC, Chattopadhyay A, Escola-Gil JC, et al. Apolipoprotein mimetics in cancer[J]. *Semin Cancer Biol*, 2020, [Epub ahead of print].
- Barter PJ, Nicholls S, Rye K, et al. Antiinflammatory properties of HDL[J]. *Circ Res*, 2004, 95(8): 764-772.
- Robbesyn F, Augé N, Vindis C, et al. High-density lipoproteins prevent the oxidized low-density lipoprotein-induced epidermal [corrected] growth factor receptor activation and subsequent matrix metalloproteinase-2 upregulation[J]. *Arterioscler Thromb Vasc Biol*, 2005, 25(6): 1206-1212.
- Tserentsoodol N, Gordiyenko NV, Pascual I, et al. Intraretinal lipid transport is dependent on high density lipoprotein-like particles and class B scavenger receptors[J]. *Mol Vis*, 2006, 12: 1319-1333.
- Prosser HCG, Tan JTM, Dunn LL, et al. Multifunctional regulation of angiogenesis by high-density lipoproteins[J]. *Cardiovasc Res*, 2014, 101(1): 145-154.
- Gao F, Vasquez SX, Su F, et al. L-5F, an apolipoprotein A-I mimetic, inhibits tumor angiogenesis by suppressing VEGF/basic FGF signaling pathways[J]. *Integr Biol (Camb)*, 2011, 3(4): 479-489.
- Rudolf M, Mir Mohi Sefat A, Miura Y, et al. ApoA-I mimetic peptide 4F reduces age-related lipid deposition in murine Bruch's membrane and causes its structural remodeling[J]. *Curr Eye Res*, 2018, 43(1): 135-146.
- Schultz JR, Verstuyft JG, Gong EL, et al. Protein composition determines the anti-atherogenic properties of HDL in transgenic mice[J]. *Nature*, 1993, 365(6448): 762-764.
- Tan JT, Ng MK, Bursill CA. The role of high-density lipoproteins in the regulation of angiogenesis[J]. *Cardiovasc Res*, 2015, 106(2): 184-193.
- Stoekenbroek RM, Stroes ES, Hovingh GK. ApoA-I mimetics[J]. *Handb Exp Pharmacol*, 2015, 224: 631-648.
- Navab M, Anantharamaiah GM, Reddy ST, et al. Apolipoprotein A-I mimetic peptides[J]. *Arterioscler Thromb Vasc Biol*, 2005, 25(7): 1325-1331.
- Bloedon LT, Dunbar R, Duffy D, et al. Safety, pharmacokinetics, and pharmacodynamics of oral apoA-I mimetic peptide D-4F in high-risk cardiovascular patients[J]. *J Lipid Res*, 2008, 49(6): 1344-1352.
- Qin S, Kamanna VS, Lai JH, et al. Reverse D4F, an apolipoprotein-AI mimetic peptide, inhibits atherosclerosis in ApoE-null mice[J]. *J Cardiovasc Pharmacol Ther*, 2012, 17(3): 334-343.
- Li X, Chyu KY, Faria NJ, et al. Differential effects of apolipoprotein A-I-mimetic peptide on evolving and established atherosclerosis in apolipoprotein E-null mice[J]. *Circulation*, 2004, 110(12): 1701-1705.
- Du L, Qu X, Zheng H, et al. Reverse apolipoprotein A-I mimetic peptide R-D4F inhibits neointimal formation following carotid artery ligation in mice[J]. *Am J Pathol*, 2013, 182(5): 1932-1939.
- Yao S, Tian H, Miao C, et al. D4F alleviates macrophage-derived foam cell apoptosis by inhibiting CD36 expression and ER stress-CHOP pathway[J]. *J Lipid Res*, 2015, 56(4): 836-847.
- Simo R, Garcia-Ramirez M, Higuera M, et al. Apolipoprotein A1 is overexpressed in the retina of diabetic patients[J]. *Am J Ophthalmol*, 2009, 147(2): 319-325.
- Small DM. Mechanisms of reversed cholesterol transport[J]. *Agents Actions Suppl*, 1988, 26: 135-146.
- Skinner ER. High-density lipoprotein subclasses[J]. *Curr Opin Lipidol*, 1994, 5(3): 241-247.
- Tserentsoodol N, Gordiyenko N V, Pascual I, et al. Intraretinal lipid transport is dependent on high density lipoprotein-like particles and class B scavenger receptors[J]. *Mol Vis*, 2006, 12: 1319-1333.
- 叶慧俊, 赵水平. ATP结合盒转运子A1与胆固醇外流[J]. *国外医学.生理、病理科学与临床分册*, 2002, 22(6): 599-601.
- YE Huijun, ZHAO Shuiping. ATP binding cassette transporter A1 and cholesterol efflux[J]. *Foreign Medical Sciences-Section of Pathophysiology and Clinical Medicine*, 2002, 22(6): 599-601.
- Girotti AW, Kriska T. Role of lipid hydroperoxides in photo-oxidative stress signaling[J]. *Antioxid Redox Signal*, 2004, 6(2): 301-310.
- Mackness MI, Durrington PN. HDL, its enzymes and its potential to influence lipid peroxidation[J]. *Atherosclerosis*, 1995, 115(2): 243-253.

24. Morgantini C, Imaizumi S, Grijalva V, et al. Apolipoprotein A-I mimetic peptides prevent atherosclerosis development and reduce plaque inflammation in a murine model of diabetes[J]. *Diabetes*, 2010, 59(12): 3223-3228.
25. Mashiba J, Koike G, Kamiunten H, et al. Vasospastic angina and microvascular angina are differentially influenced by PON1 A632G polymorphism in the Japanese[J]. *Circ J*, 2005, 69(12): 1466-1471.
26. Van Lenten BJ, Wagner AC, Jung CL, et al. Anti-inflammatory apoA-I-mimetic peptides bind oxidized lipids with much higher affinity than human apoA-I[J]. *J Lipid Res*, 2008, 49(11): 2302-2311.
27. Dai L, Datta G, Zhang Z, et al. The apolipoprotein A-I mimetic peptide 4F prevents defects in vascular function in endotoxemic rats[J]. *J Lipid Res*, 2010, 51(9): 2695-2705.
28. Smythies LE, White CR, Maheshwari A, et al. Apolipoprotein A-I mimetic 4F alters the function of human monocyte-derived macrophages[J]. *Am J Physiol Cell Physiol*, 2010, 298(6): C1538-C1548.
29. Risau W. Mechanisms of angiogenesis[J]. *Nature*, 1997, 386(6626): 671-674.
30. Tso C, Martinic G, Fan WH, et al. High-density lipoproteins enhance progenitor-mediated endothelium repair in mice[J]. *Arterioscler Thromb Vasc Biol*, 2006, 26(5): 1144-1149.
31. Seetharam D, Mineo C, Gormley AK, et al. High-density lipoprotein promotes endothelial cell migration and reendothelialization via scavenger receptor-B type I[J]. *Circ Res*, 2006, 98(1): 63-72.
32. Prosser HC, Tan JT, Dunn LL, et al. Multifunctional regulation of angiogenesis by high-density lipoproteins[J]. *Cardiovasc Res*, 2014, 101(1): 145-154.
33. Tan JTM, Prosser HCG, Dunn LL, et al. High-density lipoproteins rescue diabetes-impaired angiogenesis via scavenger receptor class B type I[J]. *Diabetes*, 2016, 65(10): 3091-3103.
34. Tan JT, Prosser HC, Vanags LZ, et al. High-density lipoproteins augment hypoxia-induced angiogenesis via regulation of post-translational modulation of hypoxia-inducible factor 1alpha[J]. *FASEB J*, 2014, 28(1): 206-217.
35. Feng Y, van Eck M, Van Craeyveld E, et al. Critical role of scavenger receptor-BI-expressing bone marrow-derived endothelial progenitor cells in the attenuation of allograft vasculopathy after human apo A-I transfer[J]. *Blood*, 2009, 113(3): 755-764.
36. Jackson JR, Seed MP, Kircher CH, et al. The codependence of angiogenesis and chronic inflammation[J]. *FASEB J*, 1997, 11(6): 457-465.
37. Di Bartolo BA, Vanags LZ, Tan JT, et al. The apolipoprotein A-I mimetic peptide, ETC-642, reduces chronic vascular inflammation in the rabbit[J]. *Lipids Health Dis*, 2011, 10: 224.
38. Prosser HC, Tan JT, Dunn LL, et al. Multifunctional regulation of angiogenesis by high-density lipoproteins[J]. *Cardiovasc Res*, 2014, 101(1): 145-154.
39. Zamanian-Daryoush M, Lindner D, Tallant TC, et al. The cardioprotective protein apolipoprotein A1 promotes potent anti-tumorigenic effects[J]. *J Biol Chem*, 2013, 288(29): 21237-21252.
40. Gkouskou KK, Ioannou M, Pavlopoulos GA, et al. Apolipoprotein A-I inhibits experimental colitis and colitis-propelled carcinogenesis[J]. *Oncogene*, 2016, 35(19): 2496-2505.
41. Su F, Kozak KR, Imaizumi S, et al. Apolipoprotein A-I (apoA-I) and apoA-I mimetic peptides inhibit tumor development in a mouse model of ovarian cancer[J]. *Proc Natl Acad Sci U S A*, 2010, 107(46): 19997-20002.
42. Cedó L, García-León A, Baila-Rueda L, et al. ApoA-I mimetic administration, but not increased apoA-I-containing HDL, inhibits tumour growth in a mouse model of inherited breast cancer[J]. *Sci Rep*, 2016, 6: 36387.
43. Samadi N, Bekele R, Capatos D, et al. Regulation of lysophosphatidate signaling by autotaxin and lipid phosphate phosphatases with respect to tumor progression, angiogenesis, metastasis and chemo-resistance[J]. *Biochimie*, 2011, 93(1): 61-70.
44. Gao F, Vasquez SX, Su F, et al. L-5F, an apolipoprotein A-I mimetic, inhibits tumor angiogenesis by suppressing VEGF/basic FGF signaling pathways[J]. *Integr Biol (Camb)*, 2011, 3(4): 479-489.
45. Zhang K, Zhang L, Weinreb R N. Ophthalmic drug discovery: novel targets and mechanisms for retinal diseases and glaucoma[J]. *Nature reviews. Drug discovery*, 2012, 11(7): 541-559.
46. Nguyen QD, De Falco S, Behar-Cohen F, et al. Placental growth factor and its potential role in diabetic retinopathy and other ocular neovascular diseases[J]. *Acta Ophthalmologica*, 2018, 96(1): e1-e9.
47. Kruger AL, Peterson S, Turkseven S, et al. D-4F induces heme oxygenase-1 and extracellular superoxide dismutase, decreases endothelial cell sloughing, and improves vascular reactivity in rat model of diabetes[J]. *Circulation*, 2005, 111(23): 3126-3134.
48. Ning R, Venkat P, Chopp M, et al. D-4F increases microRNA-124a and reduces neuroinflammation in diabetic stroke rats[J]. *Oncotarget*, 2017, 8(56): 95481-95494.
49. 谭澄焯, 邵珺, 庄森, 等. 载脂蛋白A-I对高糖环境下人视网膜血管内皮细胞生物行为及VEGF表达的抑制作用[J]. *中华实验眼科杂志*, 2017, 35(7): 586-590.
- TAN Chengye, SHAO Jun, ZHUANG Miao, et al. Inhibitory effects of apolipoprotein A-I on biological behavior and VEGF expression of human retinal epithelial cells in high glucose environment[J]. *Chinese Journal of Experimental Ophthalmology*, 2017, 35(7): 586-590.

50. Hu A, Luo Y, Li T, et al. Low serum apolipoprotein A1/B ratio is associated with proliferative diabetic retinopathy in type 2 diabetes[J]. *Graefes Arch Clin Exp Ophthalmol*, 2012, 250(7): 957-962.
51. Simó R, García-Ramírez M, Higuera M, et al. Apolipoprotein A1 is overexpressed in the retina of diabetic patients[J]. *Am J Ophthalmol*, 2009, 147(2): 319-325.
52. Miljanovic B, Glynn RJ, Nathan DM, et al. A prospective study of serum lipids and risk of diabetic macular edema in type 1 diabetes[J]. *Diabetes*, 2004, 53(11): 2883-2892.
53. Zhang J, McGwin G. Association of statin use with the risk of developing diabetic retinopathy[J]. *Arch Ophthalmol*, 2007, 125(8): 1096-1099.
54. Simó R, García-Ramírez M, Higuera M, et al. Apolipoprotein A1 is overexpressed in the retina of diabetic patients[J]. *Am J Ophthalmol*, 2009, 147(2): 319-325.
55. Curcio CA. Soft drusen in age-related macular degeneration: biology and targeting via the oil spill strategies[J]. *Invest Ophthalmol Vis Sci*, 2018, 59(4): D160-D181.
56. Sarks JP, Sarks SH, Killingsworth MC. Evolution of soft drusen in age-related macular degeneration[J]. *Eye (Lond)*, 1994, 8(Pt 3): 269-283.
57. Joachim N, Mitchell P, Burlutsky G, et al. The incidence and progression of age-related macular degeneration over 15 years: the blue mountains eye study[J]. *Ophthalmology*, 2015, 122(12): 2482-2489.
58. Sarks S, Cherepanoff S, Killingsworth M, et al. Relationship of Basal lamellar deposit and membranous debris to the clinical presentation of early age-related macular degeneration[J]. *Invest Ophthalmol Vis Sci*, 2007, 48(3): 968-977.
59. Rudolf M, Curcio CA, Schlötzer-Schrehardt U, et al. Apolipoprotein A-I mimetic peptide L-4F removes Bruch's membrane lipids in aged nonhuman primates[J]. *Invest Ophthalmol Vis Sci*, 2019, 60(2): 461-472.
60. Chun RK, Shan SW, Lam TC, et al. Cyclic adenosine monophosphate activates retinal apolipoprotein A1 expression and inhibits myopic eye growth[J]. *Invest Ophthalmol Vis Sci*, 2015, 56(13): 8151-8157.
61. Yu FJ, Lam TC, Sze AY, et al. Alteration of retinal metabolism and oxidative stress may implicate myopic eye growth: evidence from discovery and targeted proteomics in an animal model[J]. *J Proteomics*, 2020, 221: 103684.
62. Suda K, Murakami T, Gotoh N, et al. High-density lipoprotein mutant eye drops for the treatment of posterior eye diseases[J]. *J Control Release*, 2017, 266: 301-309.
63. Huerva V, Sinues B, Ascaso FJ, et al. Apoprotein A and A-I profiles in subretinal fluid[J]. *Int Ophthalmol*, 1993, 17(4): 185-189.
64. Ding N, Luo S, Yu J, et al. Vitreous levels of apolipoprotein A1 and retinol binding protein 4 in human rhegmatogenous retinal detachment associated with choroidal detachment[J]. *Mol Vis*, 2018, 24: 252-260.

本文引用: 陈珠婷, 胡洁, 胡安娣娜. 载脂蛋白A1及其模拟肽的功能及与视网膜疾病关系的研究进展[J]. *眼科学报*, 2020, 35(6): 429-435. doi: 10.3978/j.issn.1000-4432.2020.12.01

**Cite this article as:** CHEN Zhuting, HU Jie, HU Andina. Research progress on function of apolipoprotein A1 and its mimetic peptides and the relationship with retinal diseases[J]. *Yan Ke Xue Bao*, 2020, 35(6): 429-435. doi: 10.3978/j.issn.1000-4432.2020.12.01